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DIAGNOSIS AND TREATMENT OF DISEASES OF
TACTICAL IMPORTANCE TO US CENTCOM FORCES

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LTC Kelly McKee, Medical Division, USAMRIID Ft. Detrick, MD

LTC Robert A. Gasser, Jr., Infectious Disease Service
Walter Reed Army Medical Center, Washington, D.C.

MAJ Alan J. Magill, Infectious Disease Service
Walter Reed Army Medical Center, Washington, D.C.

COL Charles N. Oster, Chief, Infectious Disease Service
Walter Reed Army Medical Center, Washington, D.C.

POC: COL Michael J. Kussman, Chief Consultant In Medicine
Office of the Army Surgeon General
Falls Church, Virginia 22041

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Unit	<input type="checkbox"/>
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PREFACE TO SECOND EDITION

This Primer was developed out of a need to address medical conditions related to Operation Desert Shield. It specifically addresses communicable diseases and biological agents that medical personnel need to become familiar with and develop clinical expertise. Chemical, heat, and other topics have been covered extensively in other communications

This information is not meant to be all inclusive but to help the health care provider have access to information that is not readily available. This second edition makes some changes in the treatment of Cutaneous Leishmaniasis and expands the second section. If needed there will be further updates.

**Ronald R. Blanck
Brigadier General, MC
Director of Professional
Services
Office of the Army Surgeon
General**

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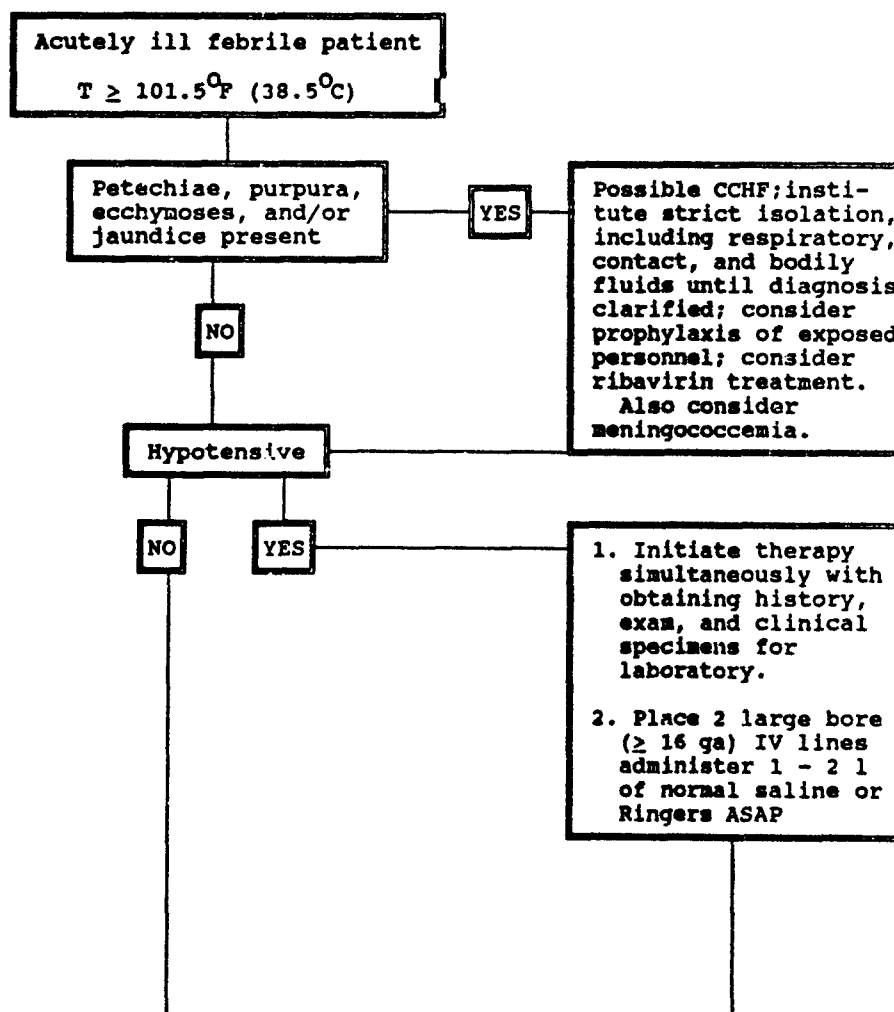
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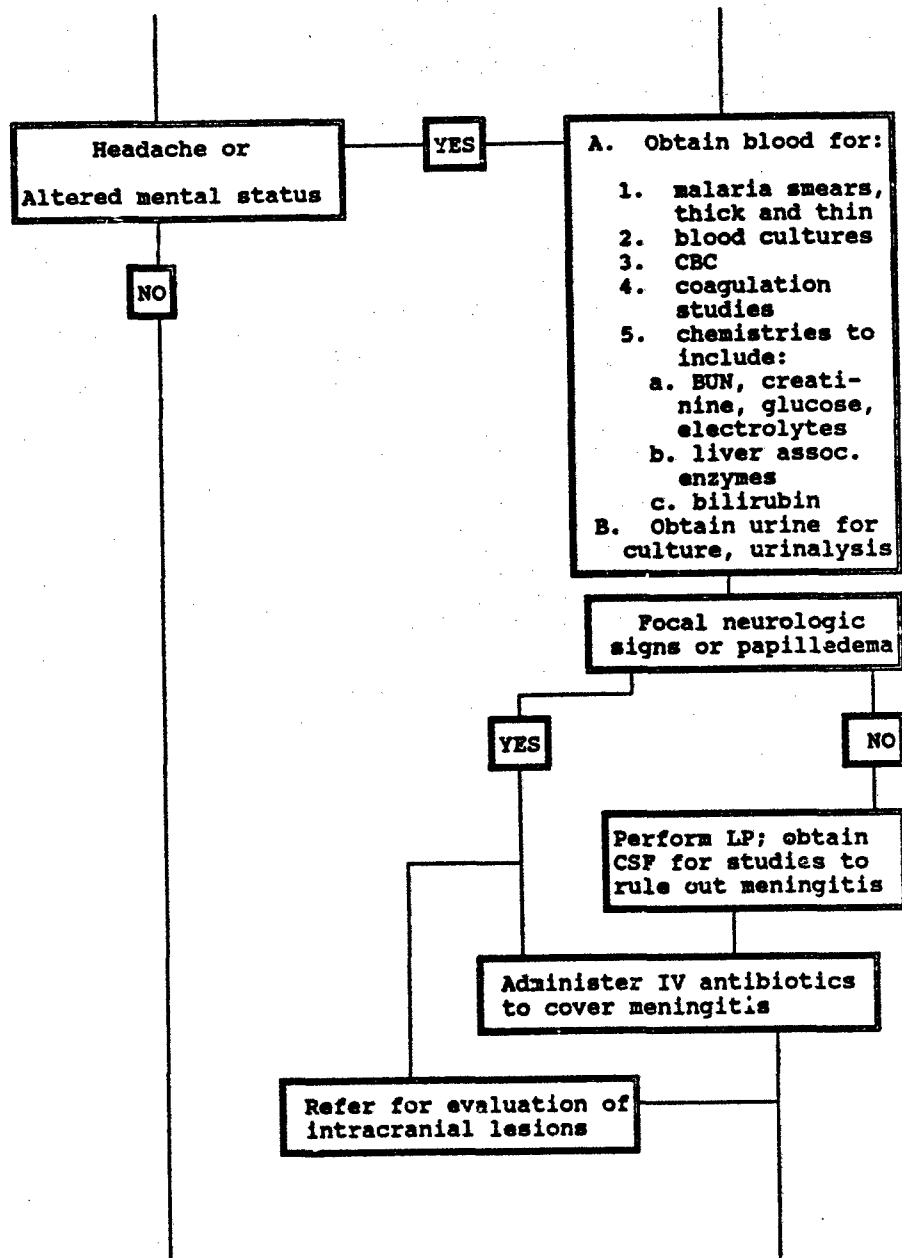
SECTION I

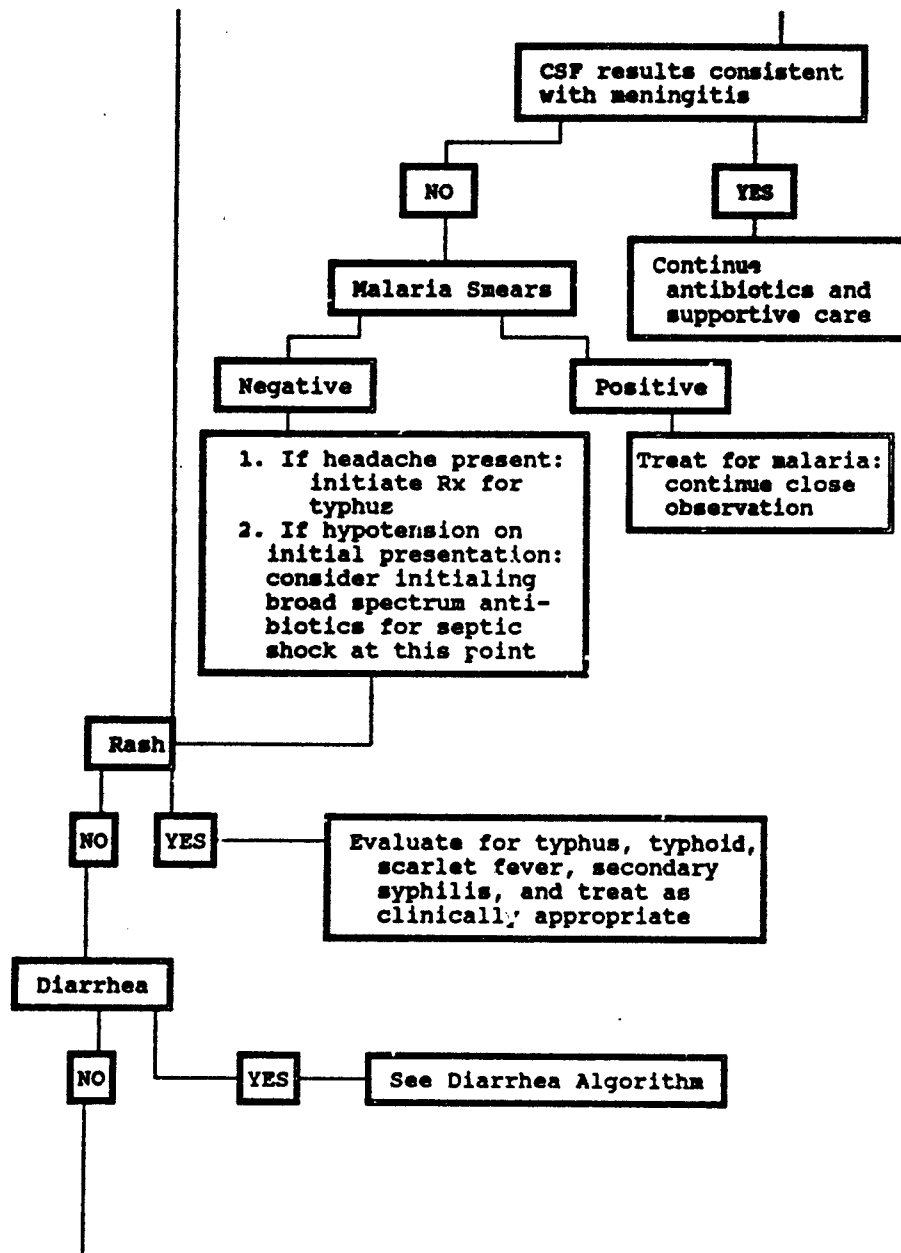
COMMUNICABLE DISEASES

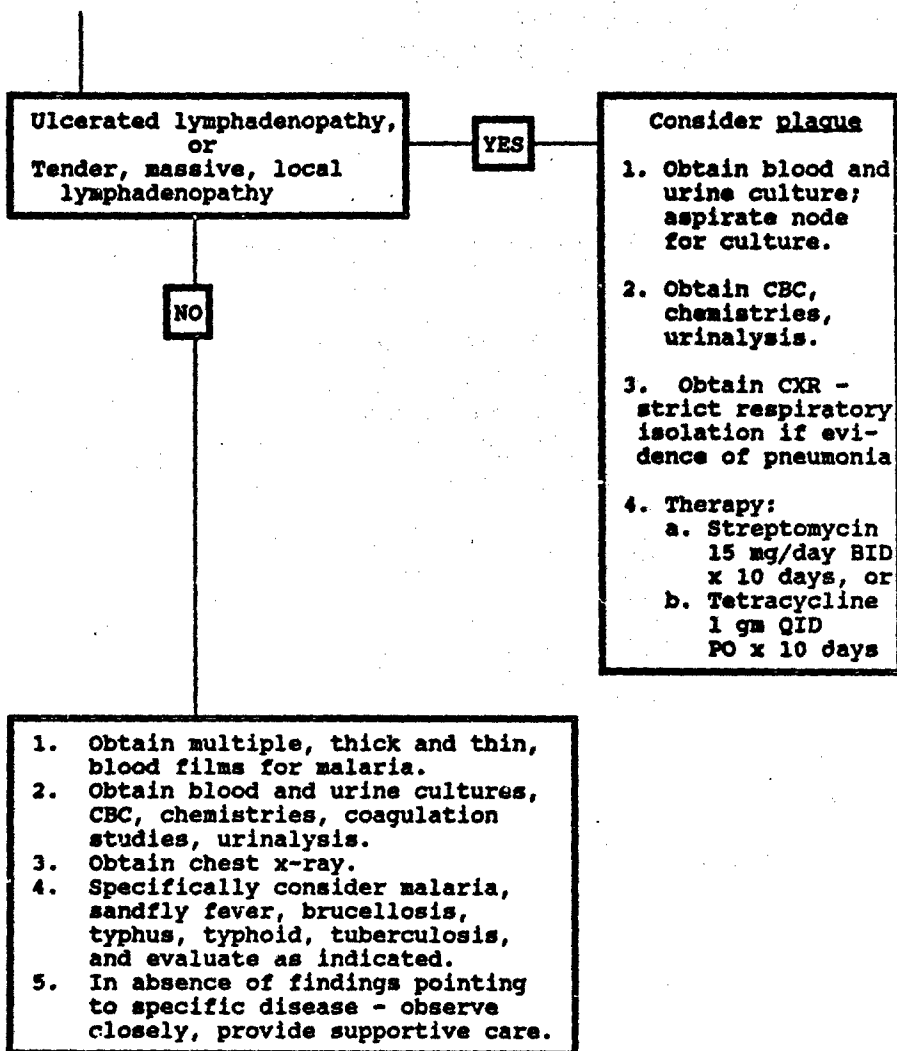
Approach to the Acutely Ill Febrile Patient

A number of infectious diseases found in the Middle East may be rapidly fatal if specific therapy is not immediately instituted. Congo-Crimean Hemorrhagic Fever may be readily transmitted to hospital personnel, with lethal consequences. The following algorithm is designed to prevent lethal oversights in the initial management of acutely ill febrile patients in the Middle Eastern environment.









BRUCELLOSIS

I. Communicability

- A. Route: inhalation of infectious aerosols; ingestion of contaminated meat or dairy products; direct contact with infected tissues, blood or lymph with abraded skin or mucous membranes.
- B. Isolation of patients: body fluid precautions.
- C. Contact prophylaxis: none required.

II. Incubation period: 2 - 3 weeks (one week to several months).

III. Diagnosis: systemic infection with protean manifestations; no diagnostic clinical findings. Exposure history is critical, ask for: (1) ingestion of unpasteurized milk products or consumption of cheese; (2) exposure to animals, livestock, meats.

A. Symptoms and signs:

- 1. Osteoarticular (20-85%):
 - arthralgias
 - myalgia
 - arthritis
 - spondylitis
 - osteomyelitis
 - tenosynovitis
 - bursitis
 - sacroileitis
- 2. Neurological (2-5%):
 - meningoencephalitis
 - myelitis
 - paresis
 - psychosis
 - depression
 - headaches
- 3. Genitourinary (2-40%):
 - unilateral epididymo-orchitis
 - pyelonephritis, acute interstitial nephritis,
 - prostatitis, (very uncommon)
- 4. Cardiovascular:
 - endocarditis - 2% (most common cause of death)
- 5. Gastrointestinal:
 - hepatitis
 - nausea and vomiting
 - diarrhea
 - abdominal pain
 - liver and spleen abscesses
 - anorexia

6. Pulmonary (15-25%):
cough
7. Systemic (almost 100%):
fever
night sweats
malaise
weakness
weight loss
8. Cutaneous (5%):
many non-specific findings such as erythema
nodosum, eczematous rashes, vasculitis, maculo-
papular rashes and petechiae.

C. Laboratory:

1. Hematology: anemia, leukopenia, thrombocytopenia
2. Microbiology: culture of pathogen from blood, bone marrow, fluids or tissue; special media, conditions and precautions required.
3. Serology: very helpful; IgM elevated in first 3 weeks, followed by IgG after 3 weeks; titer \geq 1:160 indicates past exposure.

D. Radiology:

CXR abnormal in patients who acquired infection by aerosol: hilar adenopathy; perihilar infiltrates; nodular lesions; lung abscess; pleural effusions; pneumothorax.

E. Invasive procedures: not required for diagnosis; only required in therapy for focal suppurative complications.

F. "Gold Standard:" isolation of pathogen or titer \geq 1:160 with compatible epidemiologic and clinical findings.

IV. Duration:

- A. Treated: weeks to months.
- B. Untreated: months, with up to 30% complications.

V. Complications: see signs and symptoms

VI. Treatment:

- A. No complications: doxycycline 100 mg BID plus rifampin 600 mg/day x 6 weeks.
- B. Complications: seek specialist input.
- C. Treatment failure and relapses occur in 5%; most not due to drug resistance; retreat with initial regimen.

- VII. Disposition: A. No complications: limited duty
(consider EVAC).
B. Complications: hospitalization and
EVAC.
- VII. Prognosis: A. Treated: excellent.
B. Untreated: 30% complications, prolonged
hospitalization and convalescence with
occasional deaths due to endocarditis.
- IX. Public health measures:
Locate contaminated products, if implicated, and destroy;
educate troops not to drink or eat unpasteurized dairy
products; report to Preventive Medicine. Not communicable
from person to person.

Congo Crimean Hemorrhagic Fever (CCHF)

I. Communicability:

A. Route:

1. Ixodid tick (*Hyalomma* species) bite:
2. Exposure to blood, secretions, or excrement of infected patients. Aerosol transmission may occur, as transmission to hospital staff has been documented in the absence of direct patient contact.
3. Exposure to tissue or blood of infected animals.

B. Isolation:

1. Strict isolation mandatory, to include contact, blood, body fluids, and respiratory. This must include strict precautions in handling of clinical laboratory specimens.

C. Prophylaxis:

1. No prophylaxis of proven efficacy is available.
2. Hyperimmune convalescent serum:
 - a. Isolated clinical reports suggest that administration of hyperimmune convalescent human serum may be protective. Definitive indications and dosage regimen have not been established.
 - b. 250 ml administered IV over 1 to 2 hours, possibly repeated once in 12 hours may be beneficial.
 - c. Potential problems include:
 - i. Inability to ascertain antiviral titers in transfused serum.
 - ii. Hypersensitivity reactions.
 - iii. Transmission of other blood-borne illnesses.
3. Ribavirin:
 - a. Ribavirin, an antiviral drug, may be effective. Definitive clinical studies have not yet been accomplished but preliminary studies show promise.
 - b. Post exposure prophylaxis should be strongly considered for health care workers and transporting personnel involved in caring for patients with CCHF. Prophylaxis should be begun as soon as possible after exposure.
 - c. Suggested post-exposure prophylaxis dosage regimen: 400 mg PO Q6h for 24 hours, then 400 mg PO TID for 6 days.
 - d. Adverse effects include: teratogenicity, possible embryotoxicity, reversible macrocytic anemia, extravascular hemolysis,

reversible hyperbilirubinemia, hyperuricemia, nausea, headache, insomnia, lethargy, and mood alterations. Overall, however, the drug appears safe and generally well tolerated.

II. Incubation: 7 days (range: 3-16 days).

III. Diagnosis:

A. Symptoms:

Prodromal flu-like syndrome
Abrupt onset of severe illness
Fever - 100%
Anorexia - 100%
Bleeding tendency - 100%
Headache - 90%
Abdominal Pain - 90%
Backache - 90%
Arthralgia/myalgia - 70%
Diarrhea - 40-50%
Photophobia - 50%
Cough (non-productive) - 16-40%
Chest pain - 20%
Sore throat - 16%

B. Signs:

Fever: to 40°C (104°F) - 100%
Skin hemorrhages (petechiae, purpura) - 100%
Jaundice - 25-100%
Hematuria - 90%
Tachycardia - 70-90%
Hypotension - 70-90%
Oliguria - 80%
Hepatomegaly - 80-100%
Disturbed consciousness - 80%
GI bleeding (hematemesis or melena) - 70%
Epistaxis - 50%
Vaginal bleeding >50% of women
Edema - 90%
Meningeal irritation - 40%
Bleeding gums - 40%
Relative bradycardia - 20%
Conjunctival injection - 20%
Palmar erythema - 20%
Gingival ulcers - 16%

C. Laboratory:

1. Hematologic:

Anemia (as condition deteriorates)
Leukopenia - 60%
Thrombocytopenia - 100%
Atypical lymphocytes - 60%

2. **Chemistries:**
Hyperbilirubinemia
Elevated transaminases
3. **Urinalysis:**
Hematuria - 90%
Proteinuria - 90%
4. **Microbiologic:**
 - a. Unavailable in most clinical laboratories.
 - b. Viral isolation possible by specialized laboratories with sophisticated containment and viral culture capabilities.
 - c. Exposure of laboratory personnel to aerosolized specimens is highly dangerous.
5. **Serology:** antibodies should be present by day 20, IgM earlier. Generally of retrospective and epidemiologic rather than immediate clinical value.
6. **Coagulation studies:**
Prolonged bleeding time - 100%
Prolonged PT - 75%
Prolonged aPTT - 67%
Diminished fibrinogen - 100%
Increased fibrin split products - 60%

D. **Invasive Procedures:** not applicable.

E. **X-rays:** nonspecific.

F. **Diagnostic Confirmation:** serologic or viral isolation.

IV. **Duration:**

- A. **Untreated:** 10-14 days with subsequent convalescence requiring several weeks
- B. **Treated:** undefined, but presumably shorter acute illness and markedly abbreviated convalescence

V. **Complications:**

- A. Sepsis, shock, renal failure, death.
- B. Relapse does not occur.

VI. **Treatment:**

- A. Treatment regimens of proven efficacy do not exist.
- B. **Ribavirin:** preliminary studies of ribavirin against CCHF, and clinical studies of ribavirin's efficacy against related viral hemorrhagic fevers suggest that it may be beneficial for treatment of CCHF.

1. Oral: 400 mg Q4h for 24 hours, then 400 mg Q8h for 7 to 14 days.
 2. IV: 2 gm loading dose, then 1 gm Q8h for 4 days, then 500 mg Q8h for 6 days (Dilute in saline or D5W, administer over 15 to 20 minutes).
- C. Human immune convalescent serum: isolated clinical reports suggest possible benefit. Efficacy is not proven.
1. Dosage: 250 ml, administered as single dose IV over 1 to 2 hours, and repeated Q12h as needed.
 2. Potential problems include:
 - a. Inability to ascertain antiviral titers in transfused serum.
 - b. Hypersensitivity reactions.
 - c. Transmission of other blood-borne illnesses.
- D. No alternatives exist for treatment failure.
- E. Relapses are not known to occur.
- F. Aggressive supportive care emphasizing replacement of intravascular volume and blood products is essential.

VII. Disposition:

- A. Local hospitalization is favored during acute illness if possible. If evacuation to larger facilities is unavoidable, strict isolation must be observed.
- B. Depending on clinical response, evacuation after acute illness may be required for cases showing the typical prolonged convalescence.
- C. Rapidly recovered cases may return to duty.

VIII. Prognosis:

- A. Untreated: 10-70% mortality; nosocomially acquired cases may be associated with higher mortality than sporadically required cases.
- B. Treated: unknown; inadequate data.
- C. Survivors generally suffer no major sequelae.

IX. Prevention/Public health measures:

- A. Insect repellents.**
- B. Frequent de-ticking (self-examination and removal of ticks at least BID) in infected areas.**
- C. Report suspected cases immediately to higher echelon medical authorities.**
- D. Strict isolation of cases and ribavirin prophylaxis of health care providers. (See Isolation and Prophylaxis above).**

DIARRHEAL DISEASES

I. Communicability:

- A. Route: oral ingestion of infectious organisms in contaminated food/water, particularly if inadequately cooked/purified. Inadequate personal hygiene, inadequate sanitary measures, and flies are the most likely contributory factors.
- B. Isolation of Cases: normal sanitary and stool precautions only; hand washing essential.
- C. Prophylaxis: not recommended. Efficacy is of brief duration, inadequate for sustained operations. After initial 1 to 2 weeks of protection, prophylaxis with antibiotics has been associated with increased incidence of diarrhea due to disruption of protective normal bowel flora and with emergence of drug resistant pathogens.

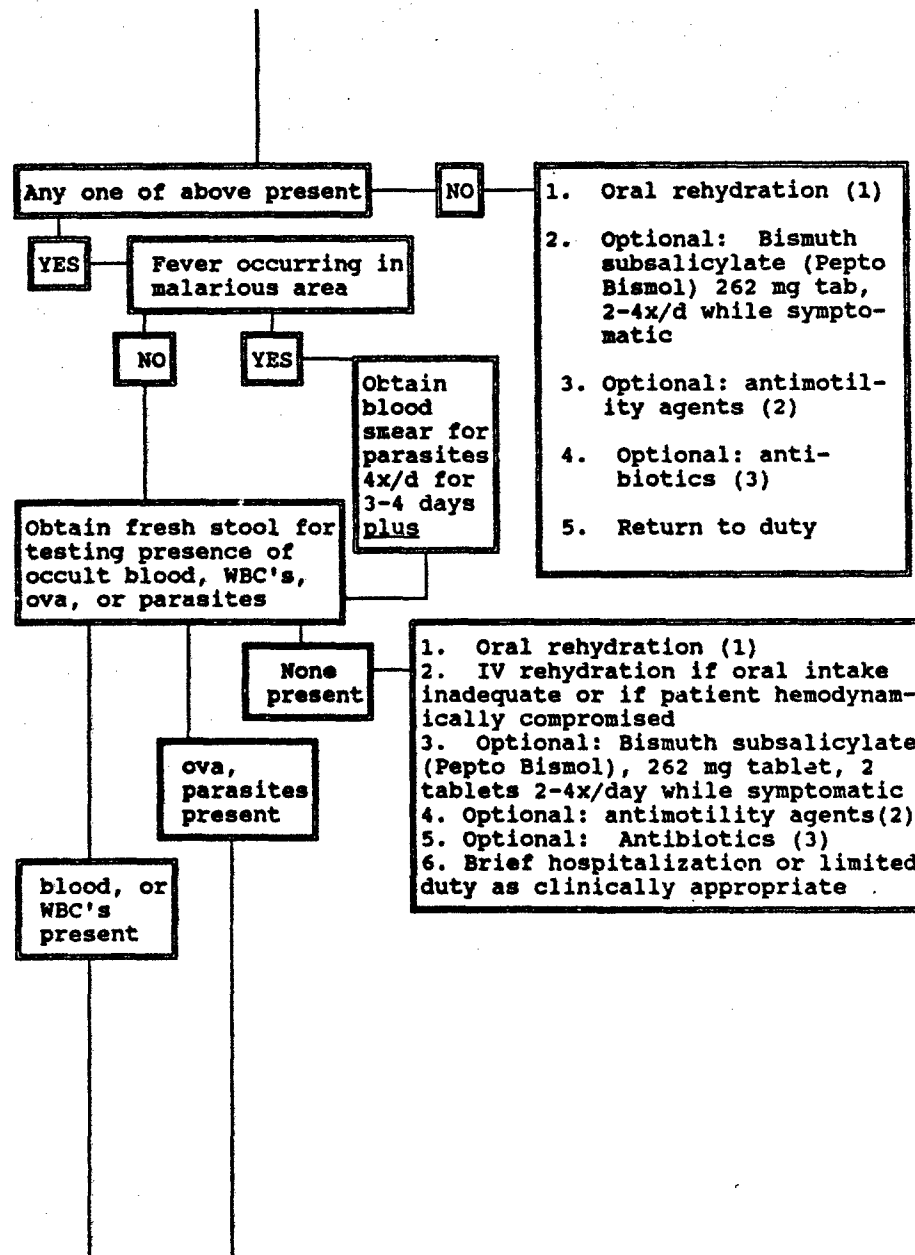
II. Incubation: varies with specific pathogen. Ranges from hours (staphylococcal enterotoxins) to several weeks (giardiasis or amebiasis).

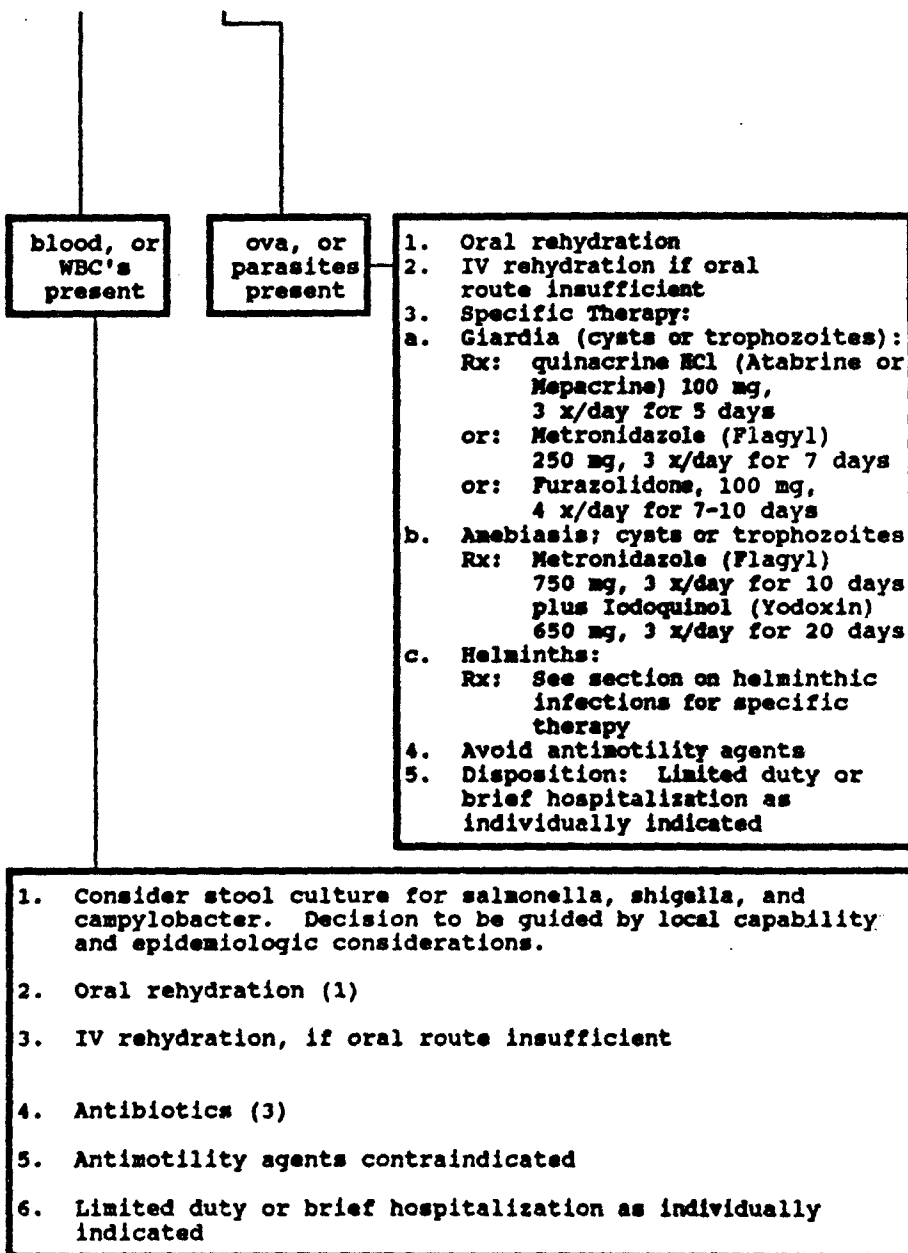
III. Diagnosis:

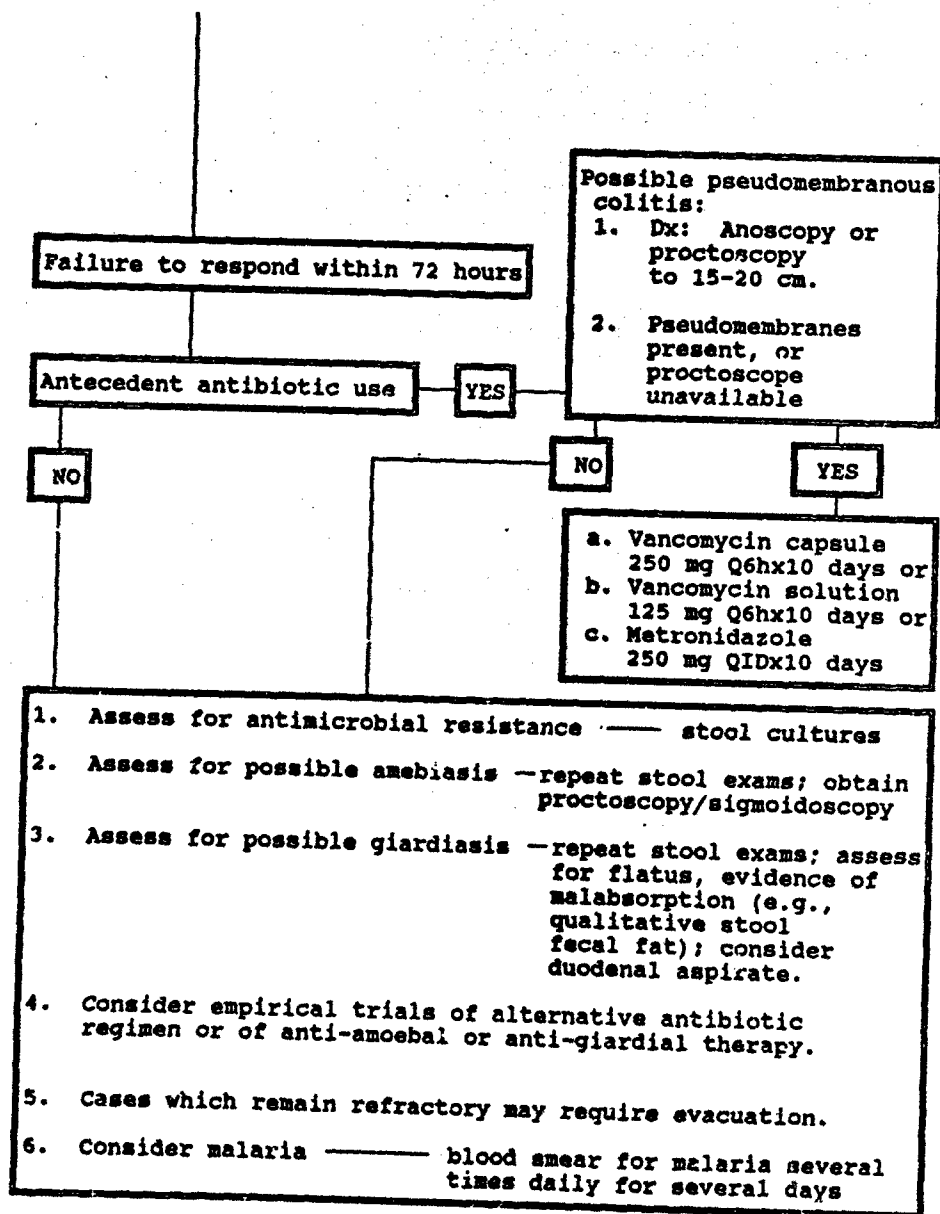
- A. Specific pathogen identification is not usually required for effective management of individual patients.
- B. The following algorithm provides an effective, efficient approach:

Symptoms: 5 stools/day, fever, abdominal pain, weight loss, blood, pus, or mucus in stool; antibiotic use in preceding 4 weeks.

Signs: fever $\geq 101^{\circ}\text{F}$; 38.3°C ; abdominal tenderness; tachycardia; hypotension; orthostatic pulse rise or blood pressure fall; guaiac positive stool.







C. Notes on the diarrhea algorithm:

1. Oral rehydration: 3.5 gm NaCl, 2.5 gm NaHCO_3 , 1.5 gm KCl, 20 gm glucose (or 40 gm sucrose) in 1 liter H_2O . Intake should be sufficient to maintain 60 to 100 ml urine output per hour. Premixed salts/glucose are available.
2. Antimotility agents:
 - a. Use Loperamide (Imodium) 2 mg tablet, 1 or 2 tablets, 2 to 4 times/day, up to 48 hours duration.
 - b. Kaopectate is ineffective.
 - c. Diphenoxylate with atropine (Lomotil) is relatively contraindicated in hot desert environment because may cause hyperthermia secondary to diminution of sweating.
3. Antibiotics: recommended regimens, in order of preference, include:
 - a. Ciprofloxacin 500 mg BID for 5 days.
 - b. Norfloxacin 400 mg BID for 5 days.
 - c. TMP/SMX 2 tablets or 1 DS tablet (for dose of 160/800 mg) BID for 5 days.

IV. Public health measures:

- A. Command emphasis on adequate sanitary facilities is essential.
- B. Command emphasis on personal hygiene, especially hand washing, is essential.
- C. Command emphasis on water purification and individual water discipline is essential.

ENTERIC FEVER (TYPHOID)

I. Communicability

- A. Route: oral ingestion of organisms, typically in contaminated food or water.
 - 1. Patients excrete organisms in stool, urine, pus and/or emesis. Asymptomatic carriage and excretion of organisms in stool is common.
 - 2. Viable organisms can contaminate food and water via spread by hands, flies, fomites, or direct contamination.
- B. Isolation of patients:
 - 1. Enteric precautions while ill and convalescing.
 - 2. Disinfection of contaminated articles.
 - 3. Since excretion of organisms typically persists for several weeks after resolution of illness, and persists more than 1 year in up to 3% of patients, convalescing patients should be evacuated rather than returned to field setting.
- C. Contact prophylaxis:
 - 1. For household (barracks or tent mate) contacts, administer vaccine if this has not been received within three years.
 - 2. Household contacts should not be used as food handlers unless both stool and urine are each negative for salmonella on two occasions at least 24 hours apart.

II. Incubation:

- A. Average: 1 week.
- B. Range: 3 days to 8 weeks.
- C. Larger inoculum is associated with briefer incubations.

III. Diagnosis:

- A. Symptoms: insidious onset
 - fever - 75-100%
 - headache - 59-90%
 - anorexia - 39-91%
 - cough - 28-86%
 - myalgia - 12-91%
 - constipation - 10-79%
 - weakness - 10-87%
 - diarrhea - 37-57%
 - vomiting - 24-54%
 - nausea - 23-54%
 - sore throat - 6-84%
 - chills - 16-37%
 - abdominal Pain - 19-39%
 - sweats - 33%

B. Signs:

1. Fever: remittent, 40°C (104°F); 75 - 100%.
2. Pulse slow relative to fever.
3. Rose spots: 2 - 4 mm blanching erythematous, maculopapular lesions; occur in crops of about 10; located on upper abdomen; lasting several hours to several days; appearing 7 - 10 days into illness; 13 - 46%.
4. Hepatomegaly: 15 - 50%
5. Splenomegaly; often tender: 40 - 64%
6. Neurologic/mental status changes: including lethargy, stupor, coma, seizures, delirium, meningismus; 10%.
7. "Pea soup" stools: loose, pale stools; 25%.

C. Laboratory:

1. Hematologic:
 - a. Hgb/Hct: anemia common, worsens progressively over first three weeks.
 - b. WBC: normal in 75% (range 1,200 - 20,000).
 - c. Platelets: usually normal, occasionally low.
 - d. ESR: typically elevated.
2. Chemistries:
 - a. SGOT, LDH: mild/moderate elevation in about 33%.
 - b. Alkaline phosphatase: mild elevation common.
 - c. Bilirubin: mild elevation (two-fold) common; sufficient to cause jaundice, uncommon.
 - d. CPK: occasionally elevated.
3. Urinalysis: nonspecific.
4. Microbiologic: causative organisms include Salmonella typhi (typhoid), other salmonella species (paratyphoid) and other bacteria including Yersinia enterocolitica, Yersinia pseudotuberculosis and Campylobacter fetus.
 - a. Blood cultures: i) first week 80% positive; by third week 20-30% positive; ii) obtain 2 to 3 sets for optimal yield.
 - b. Bone marrow aspirate cultures: 90-95% positive.
 - c. Stool cultures: occasionally positive during incubation; 33-67% positive during weeks 2 - 4 of illness.
 - d. Urine culture: intermittently positive after second week of illness in 25%. Multiple specimens should be sent.

- e. Skin snips of rose spots: may be positive when cultures of other sites fail to isolate organism.
- 5. Serologic: limited value-insensitive and non-specific.
- 6. Coagulation: usually normal. Occasionally coagulopathy, with prolonged prothrombin time (PT) and partial thromboplastin time (aPTT) may be seen.
- D. X-ray: chest x-ray normal (infiltrates in <10%).
- E. Invasive procedures:
 - 1. Bone marrow aspiration, for culture, as above.
 - 2. Skin snip or biopsy of rose spot, for culture, as above.
- F. Diagnostic confirmation: isolation of organism from blood, marrow, or skin. Isolation from stool of a typical case is presumptive evidence, but not definitive.
- IV. Duration:
 - A. Treated: 4 - 5 days, until defervescence; 2 weeks therapy required.
 - B. Untreated: 4 week acute illness, if not complicated.
- V. Complications:
 - A. Intestinal perforation:
 - 1. Incidence 1 to 10%, typically during second or third week of illness.
 - 2. Mortality: 25%.
 - 3. Signs:
 - a. classic peritoneal signs often absent.
 - b. abdominal x-ray shows free air below diaphragm.
 - c. absent bowel sounds and vomiting, suggesting ileus, may be most prominent clinical features.
 - 4. Perforations may be single or multiple.
 - 5. Ileum is most common location.
 - 6. Treatment is surgical.
 - B. GI Hemorrhage:
 - 1. Incidence: 1-20% depending on initiation of antibiotics.
 - 2. Mortality: low if recognized and treated.

3. Typically occurs during second or third week of illness.
 4. Treatment is supportive, including transfusion. Surgical intervention should be reserved for massive or persistent bleeding.
- C. Local abscess/infection:
1. Incidence $\leq 1\%$.
 2. May occur in any tissue, notably bone, soft tissue, meninges, heart, pericardium, lungs, liver, spleen, kidneys, thyroid, breast.
- D. Other complications:
1. Hemolytic anemia (2%).
 2. Typhoid pneumonia (8-10%).
 3. Peripheral neuropathy.

VI. Treatment:

- A. Preferred regimens:
1. Ceftriaxone (Rocephin): 1 gm Q12h IV for 14 days, or
 2. Ciprofloxacin: 500 mg BID orally for 14 days.
- B. Alternatives (resistance more likely):
1. Chloramphenicol: 50 mg/kg/day, divided Q6h, orally (preferred), or IV, for 14 days; or,
 2. TMP-SMX: 320/1600 to 640/3200 per day divided Q12h orally (i.e., 1 to 2 DS tablets BID, or 2 to 4 regular strength tablets BID), for 14 days.
- C. Supportive fluid and nutritional therapy is essential.
- D. Avoid heparin and antipyretics.
- E. In critically ill patients (i.e., shock, delirium, stupor, or coma): dexamethasone, loading dose 3 mg/kg IV, then 1 mg/kg q8h IV x 48 hours (improves survival from 45% to 90%).

VII. Disposition: evacuation, once stabilized.

VIII. Prognosis:

- A. Treated: $\leq 1\%$ mortality.
- B. Untreated: 10% mortality.

IX. Prevention/public health measures:

- A. Vaccinate all military personnel.**
- B. Command emphasis:**
 - 1. Strict sanitation.**
 - 2. Hand washing/personal hygiene.**
 - 3. Strict water purification/food preparation.**
 - 4. Fly control:**
 - a. insecticide spraying.**
 - b. screening.**
 - c. proper garbage disposal.**
- C. Epidemiologic investigation of each case is required.**

HELMINTH INFECTIONS

- I. A wide variety of helminths cause human disease. Specific diagnosis is based upon identification of characteristic organisms, larvae, or ova in clinical specimens. Specific treatment regimens for specific diagnoses are provided below, excluding that for schistosomiasis, which is covered elsewhere in this publication.
- II. In the face of diagnostic uncertainty as to the specific helminth in a clinical specimen, note that all round worms except strongyloides respond to mebendazole. Strongyloides is distinctive in that only larval forms, worm-like organisms approximately 220 microns (.2 mm) in length, but no ova, are seen in stool of infected patients. It responds to thiabendazole. Tapeworm infections, regardless of specific species, may be treated with praziquantel.
- II. Treatment regimens:
 - A. Roundworms (Nematodes):
 1. Ascariasis: mebendazole (Vermox) 100 mg BID orally x 3 days.
 2. Enterobiasis (Pinworm): mebendazole 100 mg orally, with a second dose 14 days later.
 3. Ancylostomiasis (Hookworm): mebendazole 100 mg BID orally x 3 days.
 4. Trichuriasis (Whipworm): mebendazole 100 mg BID orally x 3 days.
 5. Strongyloidiasis: thiabendazole 25 mg/kg BID x 2 days.
 - B. Tapeworms (Taenia species):
 1. Praziquantel 10-20 mg/kg orally, one dose.

VIRAL HEPATITIS

I. Communicability:

A. Route:

1. Hepatitis A and hepatitis E (epidemic non-A, non-B hepatitis):
 - a. Usually are contracted by oral ingestion of organisms, typically via infected food or water, or after physical contact with an infected individual (e.g., hand to hand to mouth, basically fecal-oral).
 - b. Hepatitis A is rarely spread by male homosexual activity, among IV drug abusers or by blood transfusions.
2. Hepatitis B, hepatitis delta, and hepatitis C are contracted by exposure to infected blood, blood products, other infected bodily fluids, or by sexual activity. Hepatitis delta occurs as co-infection with acute hepatitis B or as superinfection with chronic hepatitis B.

B. Isolation:

1. Hepatitis A, E: stool precautions, hand washing.
2. Hepatitis B, delta, C: needle, blood, and bodily fluid precautions.
3. In case of clinical uncertainty as to specific viral etiology, implement both types of precautions.
4. Infectiousness is generally greatest during incubation period and early icteric phase of illness, but may persist with hepatitis B or C for much longer periods.

C. Contact prophylaxis:

1. Hepatitis A, E: 2 to 5 ml of immune serum globulin (ISG) IM as soon as possible post-exposure.
2. Hepatitis B: for needle sticks or high risk sexual exposure, 5 ml Hepatitis B Immune Globulin (HBIG) IM, with simultaneous initiation of hepatitis B vaccination.

II. Incubation:

- A. Hepatitis A: 30 days (range: 15-45).
- B. Hepatitis B: 70 days (range: 30-180).
- C. Hepatitis C: 50 days (range: 15-150).

D. Hepatitis D: less well defined; probably similar to hepatitis B.

E. Hepatitis E: 40 days (range 15-60).

III. Diagnosis: the clinical manifestations of acute hepatitis caused by the various viral agents overlap. Specific diagnosis must usually be based on serology. For any type of viral hepatitis, the spectrum of disease may range from inapparent to fulminant.

A. Symptoms:

1. Malaise
2. Anorexia, including loss of taste for tobacco smoking.
3. Nausea and/or vomiting
4. Right upper quadrant pain/discomfort
5. Pruritus
6. Arthritis/Arthralgia
7. Headaches
8. Fever (low grade)
9. Jaundice
10. Dark Urine
11. Light (acholic) stools

B. Signs:

1. Icterus/jaundice
2. Tender hepatomegaly (mild-moderate)
3. Splenomegaly (uncommon)
4. Palmar erythema
5. Spider angiomas
(NOTE: fever is usually absent: if present it is low grade.)

C. Laboratory:

1. Hematologic:
 - a. Hgb/Hct: usually normal; hemolysis occurs uncommonly.
 - b. WBC:
 - i) normal or mild leukopenia.
 - ii) mild lymphocytosis with or without atypical lymphocytes may occur.
 - c. Platelets: normal.
2. Chemistries:
 - a. Transaminases:
 - i) rise 5-100x above normal.
 - ii) ALT (SGPT) > AST (SGOT)
 - b. Bilirubin: rises 1-20x normal.
 - c. Alkaline phosphatase: rises mildly, 1-4x normal.
 - d. Albumin/globulin: remains normal or near normal in uncomplicated acute hepatitis.

3. Urinalysis:
 - a. positive for bile.
 - b. occasional microhematuria.
 - c. occasional mild proteinuria.
4. Microbiologic: not applicable.
5. Serology:
 - a. Anti-Hepatitis A IgM suggests acute hepatitis A.
 - b. Anti-Hepatitis A IgG indicates prior infection with hepatitis A.
 - c. Hepatitis B surface antigen (HBsAg) indicates active infection with hepatitis B.
 - d. Hepatitis B "e" antigen indicates early stage of hepatitis B with active viral replication and greater infectiousness.
 - e. Anti-Hepatitis B surface antibody appears during convalescence; it indicates prior infection, and is not useful for directly diagnosing active hepatitis.
 - f. IgM anti-Hepatitis B core antibody indicates acute infection with Hepatitis B.
 - g. Anti-Hepatitis C antibody indicates prior infection with Hepatitis C. It is not useful for directly diagnosing active hepatitis.
6. Coagulation:
 - a. generally normal in uncomplicated acute viral hepatitis.
 - b. Prothrombin time (PT) rises in fulminant hepatitis.

D. X-ray: non specific.

E. Invasive Procedures: not indicated.

F. Diagnostic confirmation: serologic.

IV. Duration:

A. Icteric phase: 1 to 3 weeks.

B. Convalescent phase: may require up to several months.

V. Complications:

- A. Fulminant Hepatitis:
 1. Presentation: hepatic encephalopathy, asterixis, coma, coagulopathy, death.
 2. Treatment:
 - a. Supportive to include bed rest, protein restriction.
 - b. Lactulose in sorbitol orally, if tolerated, by enema otherwise; or oral neomycin.

- B. Progression to Chronic Hepatitis: occurs rarely if ever in hepatitis A, in 5-10% of hepatitis B, and in up to 50-70% of hepatitis C.
 - C. Pancreatitis.
- VI. Treatment: no specific treatment is available for viral hepatitis. Rest is important; discontinue any nonessential medications.
- VII. Disposition:
- A. Mild cases may be hospitalized in theater as some will be able to return to duty in 2 to 3 weeks.
 - B. Evacuate moderate or severe cases.
- VIII. Prognoses:
- A. Mortality: less than 1%.
 - B. Chronic disease: see complications above.
- IX. Public health measures:
- A. Hepatitis A and E:
 - 1. Administer ISG to population at risk; 2-5 ml IM; protection is roughly 1 month/ml administered.
 - 2. Command emphasis on proper sanitation.
 - 3. Proper food preparation/water purification.
 - 4. Personal hygiene.
 - 5. Hepatitis A vaccine, if available.
 - B. Hepatitis B, delta, and C:
 - 1. Vaccinate high risk populations with Hepatitis B vaccine. Vaccination series requires 3 injections at 0, 1, and 6 months.
 - 2. Sexual abstinence or use of barrier (condom) protection.
 - 3. Screening of blood products for hepatitis B and C.
 - 4. Use of barrier precautions by health workers when dealing with blood or other body fluids.

OLD WORLD CUTANEOUS LEISHMANIASIS

An ulcerative skin disease caused by *Leishmania major* in Eastern Saudi Arabia and *L. tropica* in southwestern Saudi Arabia.

I. Communicability:

- A. Route: promastigote inoculated into skin by the bite of an infected sandfly.
- B. Isolation of patients: not required.
- C. Contact prophylaxis: not required.

II. Incubation period: usually 2 to 8 weeks, but may be years depending on initial inoculum size.

III. Diagnosis:

- A. Symptoms/signs: inflammatory papule that slowly increases in size and ulcerates. Base will crust over but the ulcer spreads under the edge of a firm and raised border. Lesions are usually on exposed skin and are rarely seen in the scalp or on the palms and soles.
- B. Demonstration of the parasite is necessary to confirm diagnosis. A small full thickness skin biopsy from the lesion's edge is performed and touch preps made which can be stained with Giemsa. The biopsy is divided into halves for culture and histology. Diagnostic support is available at the Navy and Army Forward Laboratories.
NOTE: the parasite must be demonstrated for accurate diagnosis; diagnosis based on clinical picture or serology will often be erroneous.

IV. Duration:

- A. Treated: weeks to months.
- B. Untreated: *L. major* heals spontaneously in 3-5 months; *L. tropica* heals spontaneously, but takes 12 months or longer.

V. Complications: secondary bacterial infection.

VI. Treatment: ulcers do not necessarily require treatment, but consider treating if the lesions are large, multiple, threaten structures like the eye, or limit function. The diagnosis must be confirmed parasitologically before treatment is offered (see above).

1. The recommended first line therapy of uncomplicated (not interfering with function and not cosmetically disfiguring) is ketoconazole, 600 mg PO QD for 28 days (Note: this recommendation is a different than the original guidance provided in "Diagnosis and Treatment of Diseases of Tactical Importance to U.S. CENTCOM Forces, 1990"). This treatment can be administered in theater. Based on data from Panama, ketoconazole treatment will be effective in about two-thirds of the patients with cutaneous leishmaniasis.
2. Patients who do not respond (lesion doubles in area during treatment or has not reduced by 75% in area by four weeks after the end of treatment) or relapse (lesion re-ulcerates after healing or increases in size after initial reduction) after ketoconazole treatment, and patients with complicated initial disease, must be evacuated to CONUS facilities experienced in treating leishmaniasis and that have an approved protocol for the use of sodium stibogluconate (Pentostam, Burroughs Wellcome, UK). Currently, the only facility with an approved protocol is Walter Reed Army Medical Center (WRAMC), Washington, D.C. The sodium stibogluconate (Pentostam) regimen used is 20 mg/kg/day IV x 20 days.

VII. Disposition:

- A. Evacuate all patients to CONUS if sodium stibogluconate therapy is required.
- B. Report all cases through Preventive Medicine channels.

VIII. Prognosis: excellent.

IX. Public health measures:

- A. Sandfly control with residual insecticides.
- B. Host (gerbil) control.
- C. Personal protection with clothing, insect repellent.

VISCERAL LEISHMANIASIS

I. Communicability:

A. Route:

1. Sandfly (*Phlebotomus* species) bites.
2. Isolated instances of sexual transmission have been reported.
3. Isolated cases of transmission by infected blood transfusion have been reported.
4. Disease transmission by accidental inoculation in the laboratory has occurred.
5. Vertical transmission from mother to fetus has been reported.

B. Isolation: generally not required; in forward areas or under field conditions where continued exposure to sandflies may occur, personal measures to protect the patient from sandfly bites, including insect repellents and permethrin-impregnated netting, should be used.

C. Prophylaxis: not required.

II. Incubation: normally 3-8 months (range 10 days - 34 months or longer).

III. Diagnosis:

A. Symptoms:

1. Onset may be insidious (more common) or abrupt.
2. Fever: high intermittent or remittent, not generally associated with chills or prostration.
3. Sweats.
4. Cough.
5. Epistaxis.
6. Abdominal discomfort and/or swelling.
7. Weight loss.
8. Diarrhea.
9. Peripheral edema (late).
10. Bleeding diathesis (late).
11. Generalized weakness (as emaciation progresses).

B. Signs:

1. Weight loss/emaciation.
2. Splenomegaly (presents early, progressively worsens).
3. Hepatomegaly (less pronounced than splenomegaly).
4. Lymphadenopathy (especially femoral, inguinal, but may be generalized).
5. Fever (39 to 40°C).

6. Skin:
 - a. trophic changes (due to malnutrition): thinning, dryness, hair loss, hypopigmentation.
 - b. polymorphic lesions: papules, wart-like nodules, ulcers (rare).
 - c. petechiae, purpura, bruises.
7. Eye: retinal hemorrhage, papilledema, eyelid nodules, anterior uveitis.
8. Jaundice (in advanced disease).
9. Nodules or ulcers of oral and/or nasopharyngeal mucosa (rare).
10. Edema (typically late).
11. Bleeding: epistaxis, gingival, vaginal, other sites.
12. Ascites (advanced disease).

C. Laboratory:

1. Hematologic:
 - a. anemia (normochromic, normocytic).
 - b. marked leukopenia (95% with WBC < 3000/mm³).
 - c. thrombocytopenia.
 - d. Coombs test, usually positive.
 - e. marked decrease or absence of eosinophils.
 - f. parasitemia may be occasionally detected on peripheral blood smear.
 - g. buffy coat smears may be diagnostic.
2. Chemistries:
 - a. polyclonal hypergammaglobulinemia.
 - b. positive rheumatoid factor.
 - c. hypoalbuminemia.
 - d. elevated transaminases.
 - e. hyperbilirubinemia (advanced disease).
3. Urinalysis:
 - a. proteinuria (occasional).
 - b. hematuria (occasional).
4. Microbiologic: standard microbiologic techniques are not applicable.
5. Serologic:
 - a. ELISA is most sensitive (98%) but is non-specific.
 - b. indirect immunofluorescent antibody tests may be more readily available (95% sensitive).
 - c. complement fixation, counter-immunoelectrophoresis, hemagglutination, and agglutination tests are less specific.
6. Coagulation:
 - a. bleeding and clotting times are generally normal.
 - b. prothrombin time (PT) may be mildly prolonged (2 to 4 seconds more than control).

D. X-ray:

1. Standard examinations are nonspecific.
2. Hepatomegaly and splenomegaly can be detected by appropriate imaging modalities (sonogram, CT, etc.).

E. Invasive procedures:

1. Bone marrow aspiration with Wright or Giemsa stains of smear (54-86% sensitive).
2. Splenic aspiration with Wright, Giemsa, or Leishman's stain of smear (98% sensitive).
 - a. contraindications include: physician inexperience; soft spleen in acute disease; PT prolonged 5 seconds or more above normal, platelet count below 50,000/mm³.
3. Liver biopsy/aspiration: sensitivity similar to splenic aspiration, but higher risk of hemorrhage.
4. Lymph node aspiration/biopsy: less sensitive than above tests. Avoid femoral or inguinal nodes because they are less likely to be diagnostic.

F. Skin testing: Leishmanin skin test will be negative in active disease and is not useful for diagnosis.

G. Diagnostic confirmation:

1. The diagnosis must be confirmed by the demonstration of parasites in a bone marrow aspirate or biopsy.
2. Culture of organism from tissue aspirate/specimens is possible with specialized techniques (NNN or Schneider's media), but this should only be attempted at facilities with experience in culturing leishmania.

IV. Duration:

A. Treated: varies with therapeutic regimen; generally about 1 month with sodium stibogluconate (Pentostam) therapy; however, fever will respond within 48 to 72 hours of starting therapy, and the patient will feel improved within the first week.

B. Untreated: indefinite; usually fatal in months.

V. Complications:

A. Renal:

1. Renal amyloidosis with nephrotic syndrome.
2. Immune-complex mediated glomerulonephritis.

- B. Hepatic:
 - 1. Acute liver failure may rarely occur.
 - 2. Cirrhosis (rare).
- C. Disseminated intravascular coagulation (DIC).
- D. Hemorrhage.
- E. Secondary infections (common, due to immunosuppression).
 - 1. Tuberculosis.
 - 2. Pneumonia.
 - 3. Dysentery.
 - 4. Measles, in previously unvaccinated individuals.
- F. Persistent post-disease splenomegaly.

VI. Treatment: visceral leishmaniasis is a life threatening disease; therefore, all patients with suspected or confirmed visceral leishmaniasis must be evacuated to CONUS facilities (WRAMC). These patients should not be treated in theater or in Europe.

- A. Standard therapy:
 - 1. Sodium stibogluconate (Pentostam), 20 mg/kg IV QD, for 30 days. Some recommendations in past have advised not exceeding a maximal daily dose of 850 mg; however, if the dose does not exceed 20 mg/kg/day, toxicity is not excessive, and efficacy may be improved.
 - a. Drug toxicity includes: coughing, nausea, vomiting, arthralgias, myalgias, diarrhea, rash, headache, lethargy, renal toxicity, hepatic toxicity, brady-dysrhythmias, QT segment prolongation, ST segment abnormalities, T-wave inversion, and cardiac arrest (rare, to be anticipated only at dosages higher than those advised here).
 - 2. Sodium stibogluconate is not a licensed product in the United States; it must, therefore, only be given under a protocol. Currently, the only DoD facility with an approved protocol is the Walter Reed Army Medical Center.
- B. Alternatives:
 - 1. Because of their greater toxicity, alternative regimens are generally reserved for treatment failures or relapses. Such cases should be referred to tropical disease or infectious disease specialists for management.

2. Pentamidine isethionate, 4 mg/kg IM or IV, 3 times per week. The duration of therapy is not well defined; five weeks is minimum and probably inadequate. Four months is advised. Daily therapy is unacceptably toxic.

a. Drug toxicity includes: hypoglycemia, permanent drug-induced diabetes mellitus, and possible cardiovascular collapse. Lesser effects include headaches, nausea, vomiting, flushing and sterile abscesses after IM injections.

3. Amphotericin B, to a cumulative dose of 1.5 to 2.0 grams. Drug is suspended in D5W (not saline) and administered IV. Initiate therapy with a test dose of 1.0 mg administered over 15 to 20 minutes with monitored vital signs Q 30 minutes for 4 hours. Repeat dose daily, advancing to a daily dose of 0.5 mg/kg by day 5 of therapy and continuing until total desired dose has been administered or toxicity as become unacceptable.

a. Toxicity includes renal damage, electrolyte abnormalities, fever, anemia, abdominal pain, nausea, anorexia, and vomiting.

4. Additional regimens including combinations of drugs and/or gamma interferon may be used in refractory cases.

C. Treatment Failure/Relapses: refer for specialist evaluation and management, as described above.

VII. Prognosis: generally good; mortality usually occurs only in advanced disease, but even advanced disease may be successfully cured. Therapy, particularly when pentamidine or amphotericin is required, may result in permanent morbidity.

VIII. Disposition: evacuate all patients with suspected or confirmed visceral leishmaniasis. This disease is slowly progressive and should not be so far advanced in U.S. military personnel that emergency treatment is required.

IX. Public health:

A. Command emphasis on use of personal protection (repellent, impregnated netting, application of permethrin insecticides to clothes and netting if not previously treated).

B. Insecticide applications to sandfly habitats located near troop areas.

- C. Control of wild canids (foxes and jackals are the natural reservoirs of infection).
- D. Protection of patients from further sandfly bites, thus aborting possibility of epidemics based on human reservoirs.
- E. Report all cases through Preventive Medicine channels.

MALARIA

I. Communicability:

A. Route:

1. Disease is transmitted by bites of infected anopheline mosquitoes.
2. Transfusion of malaria-infected blood will transmit disease.
3. IV drug abusers sharing contaminated needles have become infected.

B. Isolation: Malarious patients must be protected from exposure to additional mosquito bites. Insect repellent and netting should be used. No other isolation is required.

C. Contact prophylaxis: prophylaxis of individuals who have had contact with malaria patients is not required per se.

D. Chemoprophylaxis:

1. Chemoprophylaxis of all individuals present in malaria areas should be instituted. At this time, malaria is not known to be present in eastern Saudi Arabia, Kuwait, or southern Iraq; however, malaria may be introduced into these areas by migrant workers or troops. Imported cases are seen in this group. *P. falciparum* and *P. vivax* malaria are seen in western Saudi Arabia. Chloroquine-resistant strains, if present, are rare.
2. a. Recommended regimen (for western Saudi Arabia): chloroquine phosphate (Aralen), 500 mg weekly, preferably commencing 1-2 weeks before arrival, and continuing for 6 weeks after departure.
b. "Terminal prophylaxis" to eradicate persistent hepatic parasites should be considered for individuals who are not pregnant or G6PD deficient: primaquine phosphate, 26.3 mg PO QD, for 14 days after departure from malaria area. In individuals unable to take primaquine, an additional 6 weeks (for total of 3 months) prophylaxis with chloroquine may be given after departure. Terminal prophylaxis should only be recommended if *P. vivax* or *P. ovale* infections have been identified in the theater.

II. Incubation:

- A. *P. falciparum*: 12 days (range 9-14).
- B. *P. vivax*: 14 days (range 12 days - 10 months).

III. Diagnosis:

A. Symptoms:

- 1. Syndrome of malaise, fatigue and myalgia may precede febrile paroxysm by several days.
- 2. Abrupt onset: fevers, chills/rigors, profuse sweats, headache, backache, myalgia, abdominal pain, nausea, vomiting, diarrhea (may be watery and profuse in *P. falciparum*).

B. Signs:

- 1. Intermittent fever to $\geq 40^{\circ}\text{C}$ (105°F). Fever may be almost continuous in *P. falciparum* malaria; classic "periodicity" is frequently absent. Profuse sweating between febrile paroxysms. Tachycardia, orthostatic hypotension, tender hepatomegaly, moderate splenomegaly, delirium (during fever).
- 2. Less common: jaundice, petechiae, urticaria, conjunctival injection, retinal vasospasm/hemorrhage.

C. Laboratory:

1. Hematologic:

- a. Intra-erythrocytic parasites on smears of peripheral blood.
 - i) thin smears: prepare film as for normal CBC, fix in methanol, use Giemsa stain.
 - ii) thick smear-one drop of blood on a slide; with glass slide corner spread drop until it is about dime size, and print on paper below slide/smear can barely be seen; stain with Giemsa stain after well dried. **DO NOT FIX!**
 - iii) thick smear more sensitive (about 20x) for identifying parasite presence, thin film more accurate for species identification.
 - iv) smear must be obtained several times/day for several days to rule out malaria.
- b. Anemia (normochromic, normocytic, hemolytic).
- c. Leukopenia.
- d. Monocytosis ($> 10\%$).
- e. Eosinophilia not seen.
- f. Thrombocytopenia (to $\leq 50,000/\text{mm}^3$).

2. Chemistries:
 - a. Hypoglycemia (may be severe, even after treatment).
 - b. Electrolyte abnormalities, including hyperkalemia, from RBC lysis.
 - c. Elevated transaminases (alkaline phosphatase normal).
 - d. Azotemia (pre-renal).
 - e. Hyperbilirubinemia.
3. Urinalysis: generally normal; small amounts of proteinuria may occur.
4. Microbiologic: standard techniques are not applicable.
5. Serology:
 - a. Biologic false positive VDRL may occur.
 - b. Specific malarial serologic tests exist, but are of epidemiologic, not clinical, value.
6. Coagulation:
 - a. Generally normal, but prolonged prothrombin time (PT) and partial thromboplastin time (aPTT) may be seen.
 - b. Disseminated intravascular coagulation (DIC) occurs, but uncommonly.

D. X-ray: nonspecific.

E. Invasive procedures:

1. Not specifically indicated.
 2. Lumbar puncture to assess mental status or neurologic changes may show elevated opening pressure but will be otherwise normal in the absence of cerebral malaria.
 3. Lumbar puncture in cerebral malaria may show increased opening pressure, increased protein and pleocytosis, but glucose is usually normal.
- F. Diagnostic confirmation: identification of parasite on blood smears.

IV. Duration:

- A. Treated: 3 days in uncomplicated cases. May recrudesce within 4 weeks if parasite drug resistant.
- B. Untreated:
 1. *P. falciparum* often rapidly fatal in untreated non-immune patients and may recrudesce up to 2 - 4 years.
 2. *P. vivax* is rarely fatal but may relapse up to 8 years.

- V. Complications: the following complications strongly indicate infection with *P. falciparum*:
- A. Hyperparasitemia: $\geq 5\%$ of RBC's on smear parasitized; correlates with other complications, though complications can be seen with lower degrees of parasitemia.
 - B. Cerebral malaria:
 - 1. Altered mental status, personality changes, lethargy, stupor, coma or delirium.
 - 2. Neurologic impairment: hyperpyrexia, monoplegia, hemiplegia, cerebellar signs, seizures (assess for hypoglycemia).
 - 3. Treatment is directed at overall infection, although exchange transfusion may be of value.
 - 4. Mortality is high (20-50%) but survivors rarely show neurologic sequelae.
 - C. Algid malaria:
 - 1. Clinically resembles septic shock; may be associated with hypothermia.
 - 2. Treatment is directed at overall infection; intravascular volume replacement, vasopressors, and antibiotics should be added to the antimalarial regimen, as needed.
 - D. Renal Failure:
 - 1. May be pre-renal or intrarenal (ATN-like) in origin.
 - 2. Treatment:
 - a. assure adequate intravascular volume replacement.
 - b. supportive care to include dialysis if needed.
 - E. Adult respiratory distress syndrome (ARDS; non-cardiogenic pulmonary edema):
 - 1. Pathogenesis: due to increased capillary permeability and fluid extravasation. Avoiding excessive intravascular fluid administration may reduce incidence.
 - 2. Treatment is supportive, to include mechanical ventilation.
 - F. Splenic rupture/hemorrhage:
 - 1. Treatment is blood replacement and control of hemorrhage surgically.

G. "Blackwater Fever:"

1. Massive hemolysis and hemoglobinuria in the setting of *P. falciparum* malaria is traditionally called blackwater fever.
2. Incidence has decreased with use of modern antimalarials. Its occurrence has been associated with quinine use, oxidant antimalarials in G6PD-deficient patients, or possibly as the result of an atypical immune response. Other causes of massive hemolysis must be excluded.
3. Treatment includes appropriate antimalarials, transfusions and the prevention or management of acute renal failure, including dialysis in some cases.

VI. Treatment:

A. Treatment of choice:

1. As chloroquine-resistant cases are not endemic in this region, initial treatment should be: chloroquine phosphate, 1 gm orally, then 500 mg at 6 hours, 24 hours and 48 hours.
2. Depending on response, prophylaxis can then be resumed; or patient can be evacuated, and terminal prophylaxis given if needed.

B. Alternatives:

1. Critically ill patients who require IV medication can receive:
 - a. Quinidine gluconate, 10 mg/kg (max 600 mg) loading dose over 1 to 2 hrs, followed by 0.02 mg/kg/minute constant infusion for a maximum of 72 hrs. Monitor EKG and switch to oral agents when mental status clears and parasitemia < 1%.
 - b. Quinidine gluconate, 15 mg/kg (max 650 kg) loading dose over 4 hours; followed by 7.5 mg/kg over 4 hours Q8h for 7 days. Monitor EKG and switch to oral agents as above.
 - c. Quinine dihydrochloride, 650 mg IV, over 4 hours, Q8h for 7 days. Switch to oral agents as above.

C. Treatment failures or early recrudescence:

1. IV regimen of quinine or quinidine as above, or
2. Quinine sulfate, 650 mg TID for 3 days, orally, plus either; pyrimethamine-sulfadoxine (Fansidar) 3 tablets in one dose; or tetracycline, 250 mg QID for 7 days; or clindamycin, 900 mg TID for 3 days, or

3. Mefloquine, 250 mg tablets, 1250 mg (5 tablets) as a single dose.

- a. Toxicities of mefloquine: CNS effects (psychosis, confusion, and seizures) and cardiac toxicity may be seen. Avoid concurrent use of quinine, quinidine, beta-blocking agents or calcium-channel blockers.

VII. Disposition:

- A. For uncomplicated cases: local hospitalization for up to 48 hours, with limited duty for several days (until drug therapy is completed).
- B. For complicated cases, including cerebral malaria, ARDS, "Blackwater Fever," and renal failure: evacuation to third or fourth echelon facilities will be needed.

VII. Prognosis:

- A. *P. vivax*: excellent if treated; mortality low, even if untreated, and complications are rare.
- B. *P. falciparum*:
1. Untreated 25% or more will be fatal.
 2. Properly treated uncomplicated cases do well, without sequelae.
 3. The prognosis for complicated cases depends on the specific complications; however, the potential for full recovery exists even for critically ill, complicated cases who should, therefore, be managed aggressively.

IX. Public health measures:

- A. Command emphasis on personal protection measures (chemoprophylaxis, repellents and netting) in endemic areas.
- B. Mosquito control: elimination of breeding sites, larvicide applications and insecticide applications to kill adult mosquitoes.

MENINGOCOCCAL DISEASE

I. Communicability:

- A. Route:** person to person by respiratory droplets.
- B. Isolation of patients:** respiratory isolation for first 24 hours of antibiotic therapy; disinfect nasal and pharyngeal secretions and material contaminated with them.
- C. Prophylaxis of contacts:**
 - 1. Intimate and household contacts, including barracks and tent-mates should receive:**
 - a.** rifampin 600 mg PO Q12h for 4 doses, or ceftriaxone 250 mg IM, one dose, or ciprofloxacin 500 mg PO Q12h for 5 days,
plus
 - b.** meningococcal vaccine, unless this has been received within two years.
 - 2. Casual contacts need not receive prophylaxis.**

II. Incubation: 3 to 4 days (range 2 to 10 days).

III. Diagnosis: meningococcal infection may be asymptomatic, or may present as a self-limited flu-like illness (without sequelae), as meningitis, as fulminant septicemia (meningococemia) or as combined meningitis-septicemia. Clinical signs and symptoms will vary with the type of presentation.

A. Symptoms:

- 1. Meningococemia:** very abrupt onset with fulminant course:
 - fever
 - headache
 - malaise
 - diarrhea (occasionally may be severe)
- 2. Meningitis:** onset may be abrupt or subacute (several days):
 - headache
 - fever
 - malaise
 - photophobia
 - nausea/vomiting
 - back ache

B. Signs:

1. Meningococcemia:

fever
tachycardia
generalized muscular tenderness
petechiae/purpura/ecchymoses - both skin and
mucosal
hypotension
altered mental status

2. Meningitis:

headache
fever
meningismus/stiff neck
cranial nerve palsies (VI most common; also
III, VII, VIII)
altered mental status
seizure
positive Kernig's sign

C. Laboratory:

1. Hematologic:

a. Meningococcemia:

i) HGB/HCT: nonspecific.
ii) WBC: leukocytosis or leukopenia (leukopenia implies more fulminant illness).
iii) thrombocytopenia: common.

b. Meningitis:

i) HGB/HCT: nonspecific.
ii) WBC: leukocytosis more typical, leukopenia suggests sepsis/meningococcemia.
iii) platelets: usually normal - thrombocytopenia suggests sepsis/meningococcemia.
iv) CSF: see below.

2. Chemistries: nonspecific; serum glucose and protein should be obtained for comparison against CSF values.

3. Urinalysis: nonspecific.

4. Microbiologic:

a. CSF Gram stain: positive in 50-90%, including meningococcemia without clinical meningitis. Organisms may be present prior to WBC's.

b. CSF culture: positive in 50-90%, including meningococcemia without clinical meningitis.

c. Blood culture: positive in 50-60%.

d. Organisms are fragile: smears and cultures should be prepared as soon as CSF is obtained from patient.

5. Serology: not applicable.

6. Coagulation: prothrombin time (PT) and partial thromboplastin (PTT) time may be elevated in meningococcemia. Evidence of DIC, including decreased fibrinogen levels, and elevated levels of fibrin degradation products may be seen.
- D. X-ray: nonspecific.
- E. Invasive procedure:
1. In presence of meningitis or suspected meningococcemia, lumbar puncture for CSF should be performed immediately, unless papilledema or focal neurologic signs are present, suggesting intracranial mass or increased intracranial pressure.
 2. CSF should be tested for glucose, protein, cell count, gram stain and culture. Counter-immunoelectrophoresis against meningococci, pneumococci, and Hemophilus influenzae may be helpful if available.
 3. CSF results:
 - a. glucose = ≤ 40 mg/dl (in 75% of cases).
 - b. protein = 150 mg/dl (range 25-800).
 - c. WBC > 1000 cells/mm, PMN predominant (range 10-65,000; lymphocyte predominance is seen in $< 10\%$).
- F. Diagnostic confirmation: culture of organism from clinical specimen (from blood, CSF, or petechial aspirate).

IV. Duration:

- A. Treated: clinical response should occur within 48 hours. Duration of convalescence depends on severity of illness and its complications.
- B. Untreated: death may occur within minutes to hours. Mortality is extremely high.

- V. Complications: shock, disseminated intravascular coagulation (DIC), adult respiratory distress syndrome (ARDS), pericarditis including tamponade, pneumonia, diabetes insipidus, cranial nerve palsies, prolonged mental status changes.

VI. Treatment:

- A. Once meningococcal disease is suspected, treatment must proceed simultaneously with the diagnostic evaluation.
 1. Obtain rapid history and physical exam, identifying contraindications to lumbar puncture.

2. Obtain blood for hemoglobin, chemistry, coagulation and culture; place IV line.
3. Perform LP if not contraindicated.
4. Administer antibiotics:
 - a. penicillin G, 300,000 U/kg/day divided in 8 to 12 doses, to a maximum of 2 million units Q2h IV, or
 - b. if penicillin allergic: chloramphenicol 100 mg/kg/day divided in 4 doses, to a maximum of 1 gm Q6h, IV.
5. Provide hemodynamic and respiratory support as needed.
6. Proceed with more detailed history and examination; evaluate results of laboratory tests.

- B. Should laboratory evaluation of CSF reveal pneumococci, penicillin or chloramphenicol may be continued.
- C. Should CSF reveal *H. influenzae*, ceftriaxone, 1 gm q12h IV or chloramphenicol may be used. Ampicillin 200-300 mg/kg/day divided q6h IV (eg, 3gm IV q3h) may be used for *H. influenzae* proven sensitive to ampicillin.

VII. Disposition:

- A. Milder cases or cases which recover rapidly may be treated at hospitals in theater in anticipation of return to duty.
- B. Cases which initially appear more severe, become complicated, or convalesce more slowly should be evacuated after initial stabilization.

VIII. Prognosis: even properly treated cases may have 5-10% mortality. Untreated, mortality may range from 50-85%. Residual morbidity is not unusual in properly treated cases. Hearing loss may persist.

IX. Public health measures:

- A. Vaccination of susceptible populations.
- B. — Antibiotic prophylaxis of close contacts, as above.
- C. Prevent overcrowding in troop shelters, and provide them with adequate ventilation.

RABIES

I. Communicability:

- A. Route:** virus laden saliva of an infected animal introduced by a bite.
- B. Isolation of patients:** contact isolation for saliva and respiratory secretions. Transmission to attending personnel has not been documented.
- C. Contact prophylaxis:** contacts with an open wound or mucous membrane that has been exposed to the patients saliva should receive post-exposure prophylaxis.

II. Incubation period: 14 to 60 days (10 days to one year); 95% are within one year.

III. Diagnosis:

- A. Symptoms and signs:** nonspecific syndrome of malaise, fatigue, headache and fever lasting 2-10 days with pain and paraesthesia at the bite site in over 50%. Syndrome merges to an acute encephalomyelitis with apprehension and hyperactivity progressing to spasm of the swallowing muscles and hydrophobia.
- B. Laboratory:** diagnosis confirmed by specific fluorescent antibody staining of brain tissues. No useful antemortem diagnostic findings that would change management, although corneal impression smears or a skin biopsy of the neck above the hair line, stained with immunofluorescent antibody, can confirm the diagnosis.

IV. Duration:

- A. Treated:** death in weeks to months.
- B. Untreated:** death in days to weeks following onset of clinical symptoms.

V. Complications: usual multiple complications of comatose ICU patient.

VI. Treatment:

- A. No specific anti-rabies chemotherapy available; treatment is directed solely at supportive care.**
- B. Pre-exposure prophylaxis not indicated for routine deployment to the Middle East.**

C. Post-exposure prophylaxis: should be given to anyone who is bitten by dog, cat, fox or jackal and considered in any other exposure.

1. Cleanse and flush wound ASAP with copious water and soap.
2. Thorough wound cleaning and debridement under medical supervision, leaving wound open if possible.
3. Single dose of human rabies immune globulin (HRIG), 20 I.U./kg, half infiltrated into the bite site and the rest given IM.
4. Give human diploid cell vaccine (HDCV) in five 1.0 ml doses, IM, on days 0, 3, 7, 14 and 28.

VII. Disposition:

- A. Exposure: full duty with supervised HRIG and HDCV.
- B. Clinical illness: EVAC

VIII. Prognosis:

- A. Treated exposure: excellent.
- B. Treated clinical illness: uniformly fatal.

IX. Public Health:

- A. Capture and sacrifice of any animal implicated; examine brain for rabies.
- B. Education of troops to avoid stray or feral dogs, cats and wild foxes.

SANDFLY FEVER

I. Communicability:

- A. Route:**
 - 1. Sandfly (*Phlebotomus papatasi*) bites.
 - 2. No direct human to human transmission.
- B. Isolation:** not required. Protection of patients from further sandfly bites will interrupt transmission. Human viremia is present from about 24 hours prior to onset of fever until about 24 hours after fever resolves. Very fine mesh for screens or bed net (10-12 mesh/cm) required. Permethrin treatment of larger mesh mosquito nets will also make them effective barriers for sandflies.
- C. Prophylaxis of contact:** none required.

II. Incubation period: 3 - 6 days.

III. Diagnosis:

- A. Symptoms:** fever to 40°C
facial congestion
neck stiffness
supraorbital pain intense or retro-bulbar
pain with eye movement
limb stiffness
malaise/nausea/myalgias
- B. Signs:** fever
conjunctival injection
papilledema (occasional)
- C. Laboratory:**
 - 1. Hematologic: leukopenia on day 4 - 5 of fever.
 - 2. Chemistries: n/a.
 - 3. Urinalysis: n/a.
 - 4. Microbiology: n/a.
 - 5. Serology: paired sera for hemagglutination-inhibition (HI) and neutralizing antibodies (retrospective only).
 - 6. Coagulation: n/a.
- D. Invasive procedures:** lumbar puncture shows increased opening pressure and CSF pleocytosis.
- E. X-ray:** n/a.
- F. Diagnostic confirmation:** serologic.

- IV. Duration: up to 4 days, convalescence may be longer.
- V. Complications: none, though patients may have lethargy, depression and easy fatigability for weeks after recovery.
- VI. Treatment:
 - A. No specific treatment available yet.
 - B. Investigation into the potential use of ribavirin is in progress. Ribavirin, 400 mg PO Q8h x 8 days, prevented human disease after experimental challenge with sandfly fever virus.
 - C. Provide supportive care.
- VII. Disposition: limited duty or local hospitalization until fever resolves, then full duty. Occasionally, convalescence may be prolonged and some patients may require EVAC.
- VIII. Prognosis: full recovery. Single infection confers lasting immunity against same serotype.
- IX. Public health measures:
 - A. Insecticide spraying of troop quarters, emplacements and entrenchments.
 - B. Troop education.
 - C. Insect repellents - command emphasis.
 - D. Report outbreaks to higher echelon medical authorities.

ACUTE SCHISTOSOMIASIS (KATAYAMA FEVER)

I. Communicability:

- A. Route-man to man spread not seen. Disease acquired by contact with infected fresh water by swimming, wading, washing, etc.
- B. Isolation of patients: not required.
- C. Contact prophylaxis: not required.

II. Incubation period: schistosomiasis dermatitis (swimmer's itch) occurs within 24 hours of penetration of skin by the infective forked tailed cercariae. Clinical syndrome occurs 1 to 3 months later and starts with an "enteric fever" like picture which resembles typhoid fever or brucellosis.

III. Diagnosis:

- A. Exposure east of the great sand belts: S. haematobium which is not associated with an acute syndrome.
- B. Exposure west of the great sand belts: S. mansoni which could present as Katayama fever.
- C. Symptoms:
 - fever (all)
 - chills
 - sweating
 - headache
 - cough (most)
 - diarrhea (50%)
 - weight loss
- D. Signs:
 - lymphadenopathy
 - hepatomegaly (50%)
 - splenomegaly (10%)
- E. Laboratory:
 - eosinophilia up to 40% in all patients
- F. Microbiology: stool exam shows eggs in most patient with acute schistosomiasis; however, stools may be negative since eggs are present in stool only 40-55 days following infection with S. mansoni.
- G. Serology: not useful in acute cases.
- H. Radiology: not useful acutely.

- G. **NOTE:** exposure history is essential to consider the diagnosis. Absence of eosinophilia (>500 cell/mm³) excludes the diagnosis.

IV. Duration:

- A. **Treated:** aborts chronic sequelae but may not limit acute disease.
- B. **Untreated:** 2 to 4 weeks for resolution of acute symptoms.

- V. **Complications:** if not recognized or treated could present later as chronic manifestations of schistosomiasis. Rare reports of death in non-immune with a heavy primary infection.

VI. Treatment:

- A. **Prasiquantel (Biltricide):** single oral dose of 40mg/kg following a meal; may also be given in two divided doses on the same day.
- B. **Prasiquantel** may cause malaise, headache or dizziness; side effects fewer if given as two divided doses.
- C. **Other schistosome infections:** chronic infections can cause hepatic cirrhosis and intestinal polyposis (*S. mansoni*), or obstructive uropathy and bladder cancer (*S. haematobium*), so all infections must be treated, whether asymptomatic or not.

- VII. **Disposition:** limited duty or hospitalization depending on how ill; EVAC may be indicated with severe disease.

VIII. Prognosis: excellent.

- IX. **Public health:** education of soldiers to avoid exposure (swimming or wading in any fresh water).

SEXUALLY TRANSMITTED DISEASES: TREATMENT REGIMENS

I. Gonorrhea:

- A. Uncomplicated urethral, cervical, or rectal infection:
 - 1. Ceftriaxone (Rocephin) 250 mg IM one dose, followed by doxycycline 100 mg BID orally x 7 days.
 - 2. Less desirable alternatives:
 - a. Spectinomycin 2 gm IM one dose followed by doxycycline 100 mg BID orally x 7 days, or
 - b. Ciprofloxacin 500 mg one dose orally, followed by doxycycline 100 mg BID orally x 7 days.
- B. Pharyngeal infections: ceftriaxone or ciprofloxacin as above; doxycycline is not indicated.
- C. Disseminated gonococcal infections:
 - 1.
 - a. Ceftriaxone (Rocephin) 1 gm IV or IM Q12h, or
 - b. Ceftizoxime (Ceftizox) 1 gm IV Q8h, or
 - c. Cefotaxime (Claforan) 1 gm IV Q8h, or
 - d. Spectinomycin 2 gm IM Q8h
 - 2. Duration: therapy should continue until 48 hours after all symptoms have resolved.
 - 3. Following above parenteral therapy, patients should receive:
 - a. cefuroxime axetil 500 mg BID orally for 7 days, or
 - b. amoxicillin with clavulanate (Augmentin) 500 mg TID orally for 7 days, or
 - c. ciprofloxacin 500 mg BID orally for 7 days.
- D. Gonococcal meningitis:
 - 1. Ceftriaxone (Rocephin) 1 gm or 2 gm IV Q12h x 10 to 14 days, or
 - 2. Chloramphenicol 1 gm IV Q4-6h for 10 to 14 days (less desirable regimen).
 - 3. In proven penicillin sensitive cases, penicillin G, 300,000 U/kg/d in divided doses, to maximum 2,000,000 U Q2h IV for 10 to 14 days, is acceptable.
- E. Gonococcal endocarditis:
 - 1. Ceftriaxone (Rocephin) 1-2 gm IV Q12h for 4 weeks.
 - 2. In proven penicillin-sensitive cases, penicillin G, 300,000 U/kg/d in divided doses, to a maximum of 2,000,000 U Q2h IV for 4 weeks may be given.
- F. Adult gonococcal ophthalmia:
 - 1. Ceftriaxone (Rocephin) 1 gm IM, one dose, plus saline irrigation. Topical antibiotics are not sufficient.

2. Persistent cases may be treated with ceftriaxone 1 gm IM or IV QD for 5 days. Concurrent infection with Chlamydia trachomatis should be suspected if patient does not respond (see below).

II. Chlamydia Trachomatis:

- A. Urethral, cervical, and rectal infection:
 1. Doxycycline 100 mg BID orally for 7 days or
 2. Tetracycline 500 mg QID orally for 7 days or
 3. Erythromycin 500 mg QID orally for 7 days
- B. Conjunctivitis (Chlamydia trachomatis):
 1. Doxycycline 100 mg BID orally for 3 weeks, or
 2. Tetracycline 500 mg QID orally for 3 weeks, or
 3. Erythromycin 500 mg QID orally for 3 weeks.

III. Non-gonococcal urethritis: as for Chlamydia trachomatis; patients who do not respond or relapse after doxycycline or tetracycline therapy should be treated with erythromycin.

IV. Syphilis:

- A. Primary, secondary, or early latent (less than 1 year duration):
 1. Benzathine penicillin G, 2.4 million units, IM, one dose.
 2. Less desirable alternatives:
 - a. Doxycycline 100 mg BID orally for 2 weeks.
 - b. Tetracycline 500 mg QID orally for 2 weeks.
 - c. Erythromycin 500 mg QID orally for 2 weeks.
- B. Late latent syphilis (more than 1 year), cardiovascular syphilis, or gummas:
 1. Benzathine penicillin G, 2.4 million units IM, 3 doses, 1 week apart, for 3 consecutive weeks.
 2. Less desirable alternatives; to be used if neurosyphilis has been excluded:
 - a. Doxycycline 100 mg BID orally for 4 weeks.
 - b. Tetracycline 500 mg QID orally for 4 weeks.
- C. Neurosyphilis: aqueous crystalline penicillin G 2 to 4 million units Q4h IV for 14 days. No proven alternative: refer for desensitization of allergic patient. Anecdotal experience with ceftriaxone, 1 to 2 gm IM or IV QD, suggests that it may be an effective alternative to penicillin.

V. Chancroid:

A. Preferred:

1. Erythromycin 500 mg QID orally for 7 days, or
2. Ceftriaxone (Rocephin) 250 mg IM, one dose.

B. Alternatives:

1. TMP/SMX 160/800 (2 tablets or 1 double strength tablet) BID orally for 7 days, or
2. Ciprofloxacin 500 mg BID orally for 7 days, or
3. Amoxicillin plus clavulanate (Augmentin) 500 mg TID orally for 7 days.

VI. Lymphogranuloma venereum (LGV):

A. Doxycycline 100 mg BID orally for 3 weeks.

B. Alternatives:

1. tetracycline 500 mg QID orally for 3 weeks, or
2. erythromycin 500 mg QID orally for 3 weeks, or
3. sulfisoxazole 500 mg QID orally for 3 weeks.

VII. Genital Herpes Simplex:

A. Genital Herpes, first episode: acyclovir 200 mg 5x/day orally, for 7 to 10 days or until resolution (whichever is longer).

B. Herpes proctitis: acyclovir 400 mg 5x/day orally, for 10 days or until resolution (whichever is longer).

C. Genital Herpes, recurrent episode: therapy is generally ineffective. In severely symptomatic disease within 2 days of onset, consider acyclovir 200 mg 5x/day orally for 5 days or 800 mg 2x/day for 5 days.

VIII. Genital Warts:

A. Biopsy all atypical, pigmented, or persistent warts.

B. Cryotherapy, podophyllin, trichloroacetic acid or electrodesiccation are all effective topical measures.

1. Cryotherapy - liquid nitrogen.
2. Podophyllin 10%-25% in tincture of benzoin: apply total volume < 0.5 ml; wash off in 1-4 hours; repeat weekly as needed.
3. Trichloroacetic acid (80-90% solution): apply weekly as needed.

IX. Pelvic Inflammatory Disease:

- A. Strongly consider hospitalization - this is particularly advised in military setting.
- B. Parenteral regimens:
 - 1. Cefoxitin 2 gm Q6h IV plus doxycycline 100 mg BID orally, until 48 hours after clinical resolution, followed by doxycycline 100 mg BID orally for a total of 14 days.
 - 2. Cefotetan, 2 gm Q12h IV may be substituted for cefoxitin, above.
 - 3. Clindarycin 900 mg Q8h IV plus gentamicin loading dose 2 mg/kg IM or IV followed by 1.5 mg/kg Q8h IV, until 48 hours after clinical resolution, followed by doxycycline 100 mg BID orally for a total antibiotic course of 14 days.
- C. Outpatient regimen (less desirable):
 - 1. Cefoxitin 2 gm IM plus probenecid 1 gm orally, one dose plus doxycycline 100 mg BID orally for 14 days or tetracycline 500 mg QID orally for 14 days or erythromycin 500 mg QID orally for 14 days.
 - 2. Ceftriaxone (Rocephin) 250 mg IM may be substituted for cefoxitin.

X. Epididymitis: treat as for urethral gonorrhea, except for prolonging doxycycline for 10 days total.

XI. Trichomoniasis: metronidazole (Flagyl) 2 gm orally, single dose, or metronidazole 500 mg BID orally for 7 days.

XII. Pediculosis pubis (crab lice):

- A.
 - 1. Permethrin 1% creme rinse applied to affected area and washed off after 10 minutes, or
 - 2. Pyrethrins and piperonal butoxide applied to the affected area and washed off after 10 minutes, or
 - 3. Lindane 1% shampoo applied for 4 minutes then washed off (avoid during pregnancy).
- B. Pediculosis of eyelids should be treated with an occlusive ophthalmic ointment BID for 10 days to smother nits and lice.

XIII. Scabies:

- A. Lindane (1%): 1 oz of lotion or 30 gm of cream applied from neck down, covering body and washed off after 8 hours, or
- B. Crothamiton (10%) applied from neck down, washed off after 24 hours, and immediately reapplied for another 24 hours.
- C. Avoid Lindane during pregnancy.

XIV. Additional diagnostic concerns: patients may be simultaneously infected with more than one sexually transmitted disease. Evaluate all such patients with serology for syphilis at presentation and at 3 months, and for HIV at presentation, and at 3 months and 6 months after presentation.

XV. Pregnancy warnings:

- A. Avoid use of tetracycline, doxycycline, acyclovir, metronidazole, ciprofloxacin, erythromycin estolate (other erythromycins acceptable), podophyllin, and lindane in pregnancy.
- B. Erythromycin is ineffective in preventing congenital syphilis in the fetus of a syphilis-infected pregnant woman.

XVI. Treatment of sexual partners, presumptive: sexual partners of patients with the following sexually transmitted diseases should be treated presumptively: chancroid, syphilis, gonorrhea, chlamydia, other non-gonococcal urethritis, pelvic inflammatory disease, and trichomoniasis.

STREPTOCOCCAL INFECTIONS

I. Communicability:

A. Route:

1. Person to person, via respiratory or salivary droplets. Crowded living arrangements enhance transmission.
2. Food and waterborne outbreaks have occurred.

B. Isolation of patient: not warranted.

C. Contact Prophylaxis: generally not warranted. In an outbreak of streptococcal disease associated with rheumatic fever or glomerulonephritis, culture and treatment of culture-positive household contacts (barracks or tent mates) can be considered. Alternatively, prophylactic benzathine penicillin can be employed to interrupt an outbreak.

II. Incubation: 2 to 4 days for pharyngitis.

III. Diagnosis: clinical streptococcal disease may present as pharyngitis, scarlet fever, erysipelas (superficial cellulitis), or pyoderma (impetigo).

A. Pharyngitis:

1. Symptoms: sore throat, headache, fever, malaise.
2. Signs: pharyngeal redness, edema, and lymphoid hyperplasia; enlarged reddened tonsils with exudate (in 50%), tender submandibular lymphadenopathy; fever $\geq 101^{\circ}\text{F}$ (38.3°C).
3. Laboratory: mild leukocytosis, positive pharyngeal cultures.

B. Scarlet Fever:

1. Usually occurs with pharyngitis, but may be seen with streptococcal skin infections.
2. Symptoms: those of primary infected site, plus fever, rash, and occasionally marked systemic toxicity or a toxic-shock like syndrome.
3. Signs: diffuse blanching red rash, darker at skin creases, normally sparing face, palms, and soles. "Sand-paper" texture of skin is due to sweat gland occlusion. Palatal petechiae. Yellowish white coating of tongue followed by beefy red appearance of tongue.

C. Erysipelas:

1. Symptoms: chills, fever, systemic toxicity.
2. Signs: red, edematous, sharply demarcated, advancing skin lesion.

D. Impetigo:

1. Signs: pustule which enlarges into thickly crusted shallow skin ulcers, typically occurring on exposed skin areas.

IV. Duration:

- A. Pharyngitis: treated 1 to 4 days; untreated 3 to 5 days.
- B. Scarlet Fever: rash persists 4 to 5 days; subsequent desquamation persists 2 to 4 weeks.
- C. Erysipelas/cellulitis: treated; improvement in 24 to 48 hours: untreated; may proceed to fatality.
- D. Impetigo: treated; improvement within 2 to 3 days. untreated: may persist several weeks.

V. Complications:

- A. Immunologic:
 1. Rheumatic fever.
 2. Acute glomerulonephritis.
- B. Infection: septicemia, otitis media, sinusitis, mastoiditis, meningitis, brain abscess, toxic shock syndrome (all uncommon).

VI. Treatment:

- A. Pharyngitis:
 1. Benzathine Penicillin G, 1.2 million units IM one dose; preferred; or
 2. Penicillin V 250 mg PO TID for 10 days (avoid due to compliance problem); or
 3. Erythromycin 250 mg PO QID for 10 days (for penicillin-allergic patients).
- B. Scarlet fever:
 1. Treat primary source of infection (e.g. pharyngitis, skin) as appropriate.
 2. Supportive care.
- C. Erysipelas/cellulitis:
 1. Penicillinase-resistant penicillin (to cross cover possible staphylococcal etiology) IV or PO depending on severity of infection. May switch to oral agent 1 to 2 days after initiating therapy if response is good. Minimum 10 day course; or,

2. Erythromycin: 0.5 to 1 gm Q6h IV followed by 500 mg Q6h PO, once response has occurred to complete full 10 day course; or
3. Vancomycin: 1 gm Q12h IV; switch to PO erythromycin to complete 10 day course.

D. Impetigo:

1. Penicillin V 250 mg PO QID for 10 days; or,
2. Erythromycin 250 mg PO QID for 10 days.

VII. Disposition:

- A. Local hospitalization required for scarlet fever, erysipelas, or severe pharyngitis.
- B. Mild pharyngitis or impetigo may be returned to duty.
- C. Evacuation should rarely, if ever, be required unless rheumatic fever, glomerulonephritis or advanced infectious complications develop.

VIII. Prognosis: excellent if treated. Complications of untreated disease will be associated with serious sequelae in some cases. Scarlet fever and erysipelas may be fatal if not properly treated.

IX. Public health measures:

- A. No specific measures warranted under most circumstances. Investigation of outbreaks is mandatory; intervention with prophylactic antibiotics may be required.
- B. Good hygiene will minimize incidence of streptococcal skin infections.

TUBERCULOSIS

I. Communicability:

A. Route:

1. Inhalation of airborne droplet nuclei from productive cough of tuberculous patients.
2. Ingestion of infected unpasteurized dairy products.

B. Isolation: respiratory isolation indicated for patients with cough productive of bacteriologically positive (culture or smear) sputum. Appropriate antituberculous drug therapy generally renders sputum non-infectious in 2 weeks. If sputum status is unknown, isolate patient until it is determined.

C. Prophylaxis:

1. Household contacts (barracks or tent mates) should be screened with intradermal intermediate strength (5-TU) PPD.
2. PPD negative contacts: retest in 2 to 3 months.
3. PPD positive contacts:
 - a. Check chest X-ray to rule out active pulmonary disease.
 - b. If chest X-ray shows evidence of pulmonary tuberculosis, evaluate and treat for active disease (see below).
 - c. If CXR is negative or normal, consider INH prophylaxis as follows:
 - i) INH 300 mg PO QD for 6 months.
 - ii) INH prophylaxis should not be given to patients: who have had prior INH therapy; those older than age 35 years who have not had a negative IPPD within two years of the current testing; those patients with active liver disease; and those patients who have had previous adverse reactions to INH.
 - iii) delay prophylactic INH chemotherapy in pregnant women until after delivery.
 - iv) advise discontinuation of alcohol intake while on INH.
 - d. In cases of exposure to known INH-resistant tuberculosis and subsequent PPD conversion, alternative regimens include:
 - i) INH, 300 mg PO QD, for 6 months.
 - ii) rifampin, 600 mg (10 mg/kg) PO QD, for 6 months; alone.
 - iii) rifampin, 600 mg (10 mg/kg) PO QD, plus ethambutol, 15-25 mg/kg QD, for 6 months.

- iv) INH, 300 mg PO QD, plus rifampin, 600 mg (10 mg/kg) PO QD, for 6 months to 1 year.

II. Incubation:

- A. For development of primary lesion: 4 to 12 weeks.
- B. For progressive, reactivation or extrapulmonary disease: 4 weeks to lifetime. Risk of active disease is greatest during the first 6 to 24 months after infection, or with development of other systemic illnesses which weaken host defenses.

III. Diagnosis:

A. Symptoms:

- 1. Disease may be asymptomatic, especially early.
- 2. Fever (may be intermittent)
 - night sweats
 - anorexia
 - weight loss
 - fatigue
 - cough (productive or non-productive)
 - hemoptysis
 - chest pain (pleuritic)
 - dyspnea
- 3. Symptoms produced by extrapulmonary tuberculosis depend on the organ system involved. In rough order of frequency, extrapulmonary sites include:
 - a. lymphatics
 - b. pleura
 - c. genitourinary tract
 - d. bone/joint
 - e. meninges
 - f. peritoneum
 - g. other, including: liver, pericardium, middle ear and brain.

B. Signs:

- 1. Signs may be absent, especially in early disease. In general they are nonspecific and less significant than would be expected from extent of disease.
- 2. Rales, especially post-tussive; dullness to percussion; and diminished breath sounds.
- 3. Other signs depend on the site(s) of extrapulmonary involvement.

C. Laboratory:

1. Hematologic:
 - a. May be normal.
 - b. Anemia, mild leukocytosis or monocytosis ($\geq 10\%$)
2. Chemistry:
 - a. Usually normal.
 - b. Hypercalcemia.
 - c. Hyponatremia.
 - d. Other abnormalities may represent specific effects of extrapulmonary involvement.
3. Urinalysis:
 - a. Usually normal.
 - b. In presence of genitourinary tuberculosis may see sterile pyuria, proteinuria and/or hematuria.
4. Microbiologic:
 - a. Examination of smear (sputum, gastric aspirate) with acid-fast staining may show organism. A single organism on a slide may be significant, though usually 3 to 5 organisms per slide is considered a true positive.
 - i) Fluorochrome staining is most efficient.
 - ii) Alternatives include Ziehl-Neelson, Kinyoun, or blue-light fluorescent stains.
 - b. Radiometric culture system (i.e. BACTEC) will reveal presence of organisms in 2 to 6 days.
 - c. Standard mycobacterial cultures may take up to 6 weeks to define organism.
 - d. Drug sensitivity results are generally unavailable before 4 to 6 weeks.
 - e. In presence of urinary sediment abnormalities, obtain AFB smears and cultures on centrifuged urine.
5. Serology: not in general use.
6. Coagulation: generally normal.

D. X-ray: findings depend on the character and extent of disease.

1. Early or primary TB may present in any lobe (more typically lower) as pneumonic infiltrate, atelectasis or mass, with or without ipsilateral hilar adenopathy.
2. Later, chronic, or reactivation TB typically shows patchy or nodular infiltrates in the apices or superior segments of lower lobes; cavitation may or may not be present.
3. Pleural effusions may be seen.

E. Invasive procedures:

1. Gastric aspirate for smear and culture may be useful if no sputum can be produced.
2. Bronchoscopy, with washings for cultures, may be diagnostic when TB is a consideration but organisms cannot be recovered by less invasive means.
3. The choice of other specific invasive procedures, including thoracentesis, lumbar puncture, or biopsies, is guided by clinical evidence of extrapulmonary TB.

F. Skin testing: in previous non-reactors, PPD may convert to positive by 4 weeks. PPD may be negative in early or primary disease, in overwhelming disease, or in patients with immunosuppression from other disease. Up to 25% of patients with pulmonary TB may have negative skin tests; 5% of patients may have selective anergy (negative PPD and positive anergy panel). In an area of high prevalence, IPPD skin tests of >10 mm induration are considered positive.

G. Diagnostic confirmation: successful culture of mycobacteria from clinical specimens.

IV. Duration:

- A. Treated: variable, depending on extent of disease. Treatment regimens range from 9-18 months in length, but clinical response occurs much sooner.
- B. Untreated: indefinite: 50% die; 25% develop chronic TB, which can remain active for years; and 25% spontaneously heal.

V. Complications:

- A. Pulmonary: hemoptysis; massive hemorrhage; and major parenchymal lung damage with permanent impairment of respiratory function.
- B. Extrapulmonary: ranges from minor damage to destruction of the involved organ.
- C. Recurrence, possibly with resistant organisms, may occur in inadequately treated patients. Recurrence in adequately treated patients is very uncommon, but may occur.

VI. Treatment:

- A. Standard treatment is a 9 month course of INH, 300 mg QD, plus rifampin, 600 mg (10 mg/kg) QD.
- B. Given the high level of resistance to INH anticipated in organisms acquired in the Middle East, treatment of TB cases in that setting should include rifampin plus at least one other drug in addition to INH. Optimal choices for the third drug include pyrazinamide, 25-35 mg/kg (maximum 2.5 gm) QD, or ethambutol, 15-25 mg/kg QD. A four drug regimen containing INH, rifampin, ethambutol, and pyrazinamide may be optimal in this setting pending mycobacterial sensitivity results.
- C. Monitor therapy monthly.
- D. Alternative agents include:
 - 1. Streptomycin, 750 to 1000 mg IM QD for 2 to 3 months, then 750-1000 mg IM 2 to 3 times per week; resistance to streptomycin is common in the Middle East.
 - 2. Capreomycin, 1 gm IM QD; greater ototoxicity than streptomycin.
 - 3. Ethionamide, 10-15 mg/kg PO QD; bacteriostatic; has GI, hepatic, and neurotoxicity.
 - 4. Cycloserine, 750-1000 mg PO QD, divided in 3 or 4 doses; bacteriostatic; has significant potential central nervous system toxicity. Pyridoxine, 100 mg QD, should be considered to prevent CNS toxicity.
 - 5. Amikacin, 15 mg/kg IM QD.
- E. Treatment failures or relapses: therapy should be guided by mycobacterial sensitivity results, with the basic principle of always using at least two new drugs to which the organism is sensitive. Refer patients with resistant disease for specialist management. If a patient is failing on therapy, always add two new drugs until sensitivities are known.

VII. Disposition: varies with severity of clinical disease.

- A. Asymptomatic, or mildly ill patients whose symptoms resolve quickly, may be returned to duty on medication, with follow-up, once non-infectious (usually by two weeks of treatment).
- B. More seriously ill, or persistently ill, patients will require evacuation.

- C. The need for temporary isolation of infectious cases may guide the disposition decision, based on available medical capabilities.

VIII. Prognosis: excellent in properly treated cases.

IX. Public health measures:

- A. Isolation and treatment of infectious patients.
- B. Prophylaxis of contacts (see Section II, above).
- C. Avoid use of local (unpasteurized) dairy products.

ENDEMIC TYPHUS (MURINE TYPHUS, FLEABORNE TYPHUS)

I. Communicability:

A. Route:

1. Bite of infected rat flea (*Xenopsylla cheopis*).
2. No evidence of person to person transmission.

B. Isolation: not required.

C. Prophylaxis of contacts: not required.

II. Incubation: 12 days (range 4-15 days).

III. Diagnosis: overall similar to epidemic typhus but milder, briefer.

A. Symptoms: onset variable, but more commonly sudden.

fever (90-100%)
chills
headache (severe) (85% or more)
myalgia (85%)
non-productive cough (50-60%)
nausea
vomiting
marked weakness/prostration
sore throat
chest pain

B. Signs:

fever (100%) up to 40°C (105°F) for 12-16 days
duration.
rash (60-80%) initial: upper thorax and abdomen,
macular, appears on day
3-5 of illness.
later: remains central, becomes
maculopapular, duration
4-8 days, rarely involves
face or palms.
conjunctival injection (50%)
splenomegaly (30%)
mental status changes (20%)
photophobia (10-20%)
no eschar present

C. Hematology: WBC usually normal.

D. Chemistries: non-specific.

E. Microbiology: not available, except in special facilities with containment capability.

- F. U/A: proteinuria (15-20%).
 - G. Serology: Weil-Felix reaction to OX-19 (four-fold titer rise or single titer $\geq 1/320$).
 - H. Coagulation: nonspecific.
 - I. Invasive procedures: not indicated.
 - J. X-ray: findings non-specific.
 - K. Diagnostic Confirmation: clinical diagnosis generally is sufficient for patient care. If specific confirmation is required for epidemiologic purposes, culture or specialized application of indirect immunofluorescent antibody after cross absorption of patient's serum with specially prepared antigen from other rickettsial species.
- IV. Duration:
- A. Treated: 2 to 3 days, until defervescence.
 - B. Untreated: up to 16 days until defervescence.
- V. Complications: very uncommon.
- VI. Treatment:
- A. Standard:
 - 1. Tetracycline 250 mg PO QID until day 3 after defervescence.
 - B. Alternatives:
 - 1. Doxycycline 100 mg PO BID until 3 days after defervescence.
 - 2. Chloramphenicol 50 mg/kg/day divided into 4 doses until 3 days after defervescence.
 - C. Relapse: rare in murine typhus; retreat with original regimen.
- VII. Disposition: local hospitalization, anticipate return to duty in 1 to 2 weeks.
- VIII. Prognosis: excellent; even untreated cases should recover without sequelae.

IX. Public health measures:

- A. Insecticide application to rat runs and rat-infested areas to kill fleas.**
- B. After effective insecticide applications, rat-elimination measures including poisoning and trapping are indicated.**
- C. Rat-proofing human quarters.**

EPIDEMIC TYPHUS (LOUSE-BORNE)

I. Communicability:

A. Route:

1. Body louse (*Pediculus humanis*) infestation; inoculation with louse feces through skin abrasions or excoriations.
2. No evidence of person-to-person transmission.

B. Isolation: contact isolation required until after delousing (by insecticide) of patients clothing, bedding, quarters, and household contacts. Options: DDT; lindane; malathion; carbaryl.

C. Prophylaxis:

1. A killed organism vaccine is available but is recommended only for high risk individuals, not usually including military personnel. Two doses, 10 to 14 days, apart may reduce incidence of disease, and diminishes mortality to almost nil.
2. Doxycycline, single dose, 200 mg.

II. Incubation period: 12 days (range 5-23).

III. Diagnosis:

- #### A. Symptoms: abrupt onset.
- sustained fever $\geq 40^{\circ}\text{C}$
 - severe headache
 - prostration
 - back pain
 - limb pain
 - non-productive cough
 - photophobia
 - anorexia
 - constipation
 - nausea (uncommon)
 - vomiting (uncommon)
 - diarrhea (uncommon)

B. Signs:

rash (90%); onset, day 3 to 5 of illness. Initially in axillary folds, on abdomen and chest. Centrifugal spread later. Initially roseolar, macular; becomes petechial. Rarely involves palms, soles or face. No eschar is seen.

- profound lethargy/stupor
- delirium
- facial congestion
- conjunctival injection
- splenomegaly

hypotension
tachycardia
jaundice (uncommon)
oliguria
meningismus
cranial nerve palsies, including deafness/tinnitus

C. Laboratory:

1. Hematologic: leukopenia early; no eosinophilia; anemia and thrombocytopenia seen as disease advances.
2. Chemistry: azotemia, hypoalbuminemia, hyponatremia.
3. U/A: proteinuria.
4. Microbiology: culture may be possible in large centers but not under field conditions or in small hospitals.
5. Serology:
 - a. Weil Felix reaction (OX-19): 4 fold rise or single titer $\geq 1:320$ in 2nd week of illness.
 - b. Specific serologic testing: IFA or microagglutination.
6. Coagulation: prolonged prothrombin time (PT).

D. Invasive procedures: CSF may show pleocytosis.

E. X-ray: CXR may show pulmonary infiltrate.

IV. Complications: sepsis, parotitis, pneumonia; rarely myocarditis, CHF, thromboses.

V. Treatment:

- A. Doxycycline, 200 mg PO, single dose.
- B. Tetracycline, 250 mg PO QID, until 3 days post defervescence (avoid if renal failure is present).
- C. Chloramphenicol, 50 mg/kg/day, divided into 4 doses, until 3 days post defervescence.
- D. Relapse: repeating initial treatment is effective.

V. Disposition:

- A. Initial: hospitalization.
- B. Post treatment: prompt responders, return to duty; complicated cases, with those with inadequate response to treatment: evacuate.

VI. Prognosis:

- A. Mortality:
 - 1. Treated: very little, if any, mortality.
 - 2. Untreated: 10-40% depending on clinical situation.
- B. Prompt recovery with therapy: usually better in 24 to 48 hours.
- C. Untreated: fever lyses in 2 weeks; mentation rapidly returns to normal; 2 to 3 months may be required for return of strength.
- D. Relapses occur rarely, but are more likely if tetracycline or chloramphenicol are prematurely stopped.

VII. Prevention:

- A. Insecticides:
 - 1. Application of insecticide to clothing of all personnel at risk of exposure.
 - 2. Use of persistent insecticide for application to clothing of individuals at particular risk.
- B. Hygiene: command emphasis on personal hygiene and cleanliness of clothing.
- C. Disease reporting to higher echelon medical authorities.

**DIAGNOSIS AND TREATMENT OF EXOTIC DISEASES
OF TACTICAL IMPORTANCE TO US CENTCOM
FORCES-1991**

**U.S. ARMY MEDICAL RESEARCH INSTITUTE
OF INFECTIOUS DISEASES
FORT DETRICK
FREDERICK, MARYLAND 21702-5011**

POC: LTC KELLY McKEE

INTRODUCTION

Biological warfare is the use of microorganisms or toxins derived from living organisms to produce death or disease in humans, animals, or plants. In spite of the 1972 Biological Weapons Convention prohibiting the use of biological warfare agents, concern over compliance remains. Information from earlier offensive programs clearly has demonstrated the vulnerability of inadequately protected troops to such agents. This experience, coupled with advances in modern technology, makes it possible that allied forces may be exposed to biological weapons. Characteristics of many live agents and toxins make them potentially effective for offensive military use. These agents can provide a readily available and effective weapon in the hands of terrorists as well as assassins.

Section I of this document (below) provides general background information and principles applicable to some biological threats. Outlined in Section II is an assessment of our current capability to respond to several of the recognized threat agents. A common format is used to enable rapid consolidation of capabilities by response area (e.g., specific laboratory diagnosis, therapy, prophylaxis). Section III contains information pertinent to specimen collection and processing for the specific laboratory diagnosis of biological warfare threat agents. Section IV provides a review of clinical features distinguishing chemical neurointoxications from botulism and SEB, and pulmonary syndromes that can be seen in chemical and biological warfare exposures.

SECTION I

ROUTES OF EXPOSURE

Inhalation: Biological weapons are dispersed as aerosols by one of two basic mechanisms: point- or line-source dissemination. Unlike some chemical threats, aerosols of agents disseminated by line-source munitions (e.g., sprayed by low-flying aircraft or speedboat along the coast) do not leave hazardous environmental residues (although anthrax spores may persist and could pose a hazard near the dissemination line). On the other hand, aerosols generated by point-source munitions (i.e., stationary aerosol generator, bomblets, etc.) are more apt to produce ground contamination, but only in the immediate vicinity of dissemination. Point-source munitions leave an obvious signature that alerts the field commander that a biological warfare attack has occurred. Because point-source munitions always leave an agent residue, this evidence can be exploited for diagnostic purposes.

Aerosol delivery systems for biological warfare agents most commonly generate invisible clouds with particles or droplets of < 10 micrometers (μm). They can remain suspended for extensive periods. The major risk is pulmonary retention of inhaled particles. To a much lesser extent, particles may adhere to an individual or his clothing. The effective area covered varies with many factors, including wind speed, humidity, and sunlight. In the absence of an effective real-time alarm system or direct observation of an attack, the first clue would be mass casualties fitting a clinical pattern compatible with one of the biological

agents. This may occur hours or days after the attack. Toxins may cause direct pulmonary toxicity or be absorbed and cause systemic toxicity. Toxins are frequently as potent or more potent by inhalation than by any other route. A unique clinical picture may sometimes be seen which is not observed by other routes [e.g., pulmonary edema after staphylococcal enterotoxin B (SEB) exposure]. Mucous membranes, including conjunctivae, are also vulnerable to many biological warfare agents. Physical protection is then quite important and use of full-face masks equipped with small-particle filters (e.g., M17-A1, M40, M43) assumes a high degree of importance.

Oral: Other routes for delivery of biological weapons are thought to be less important than inhalation, but are nonetheless potentially significant. Contamination of food and water supplies, either purposefully or incidentally after an aerosol biological warfare attack, represents a hazard for infection or intoxication by ingestion. Assurance that food and water supplies are free from contamination should be provided by appropriate preventive-medicine authorities in the event of an attack.

Dermal: Intact skin provides an excellent barrier for many but not all biological agents. Mucous membranes and abraded, or otherwise damaged, integument can, however, allow for passage of some bacteria and toxins, and should be protected in the event of an attack.

GENERAL PROTECTIVE MEASURES

Physical Protection: The most effective and most important prophylaxis in defense against biological warfare agents is physical protection. Preventing exposure of the respiratory tract and mucous membranes (to include the conjunctivae) to infectious and/or toxic aerosols through use of a full-face respirator will obviate the need for additional measures. To this end, the currently fielded chemical masks (e.g., M17-A1 and new M40 and M43) are protective if properly fitted and in use at the time of exposure.

Decontamination. Protection of Health Care Personnel: Dermal exposure from a suspected biowarfare attack should be treated by soap and water decontamination. This should follow any needed use of chemical decontaminants but should be prompt. Secondary contamination of medical personnel from clothing, etc. of exposed soldiers may be important, particularly from casualties recently exposed near the dissemination source where large particle deposition may occur. Since it will be difficult to distinguish those soldiers exposed near the source from those contaminated some distance away, proper physical protection of health care providers or other persons handling exposed personnel should be maintained until decontamination is complete. This applies to chemical exposures as well.

Clinical laboratory samples for toxin-exposed subjects can be dealt with routinely. Patients showing signs of pneumonic plague generally should be considered hazardous, as some will disperse plague bacilli by aerosol. Exposure of health care providers to open lesions or blood from anthrax patients could result in cutaneous anthrax. Vegetative forms of anthrax do not pose a threat of aerosol dissemination from blood or during autopsy

procedures, but sporulation of bacilli exposed to air will occur over time, posing a subsequent theoretical risk with inhalation. On the other hand, vegetative forms of plague and tularemia bacilli may be dangerous, since, under some circumstances, they are known to cause aerosol infections. Therefore, postmortem examinations of suspected anthrax, plague, and tularemia victims should be performed with strict mask, gown, and glove precautions because of the large numbers of organisms present in body fluids.

Prophylaxis and Therapy: All medical prophylactic modalities described should be viewed only as secondary (i.e., backup), and are not to be relied upon as primary protective measures. Agent exposures near the source of dissemination will be high, and likely to overwhelm any medical protective measure. The precise efficacy of available medical countermeasures has, of course, never been evaluated in actual field circumstances, but is largely inferred from laboratory studies on nonhuman primates. While these extrapolations may be inexact, they strongly support the efficacy of vaccines and drugs at some agent dose.

SECTION II SPECIFIC THREAT AGENTS

ANTHRAX

A: CLINICAL SYNDROME

Anthrax is a zoonotic disease caused by Bacillus anthracis. Under natural conditions, humans become infected by contact with infected animals or contaminated animal products.

Human anthrax usually is manifested by cutaneous lesions. A biological warfare attack with anthrax spores delivered by aerosol would cause inhalation anthrax, an extraordinarily rare form of the naturally occurring disease.

Clinical Features: The disease begins after an incubation period varying from 1-6 days, presumably dependent upon the dose of inhaled organisms. Onset is gradual and nonspecific, with fever, malaise, and fatigue, sometimes in association with a nonproductive cough and mild chest discomfort. In some cases, there may be a short period of improvement. The initial symptoms are followed in 2-3 days by the abrupt development of severe respiratory distress with dyspnea, diaphoresis, stridor, and cyanosis. Physical findings may include evidence of pleural effusions, edema of the chest wall, and meningitis. Chest X ray reveals a dramatically widened mediastinum, often with pleural effusions, but typically without infiltrates. Shock and death usually follow within 24-36 hours of respiratory distress onset.

B: DIAGNOSIS

1. Routine Laboratory Findings: Laboratory evaluation will reveal a neutrophilic leukocytosis. When pleural effusions and evidence of meningitis are present, pleural and cerebrospinal fluids may be hemorrhagic.

2. Differential Diagnosis: An epidemic of inhalation anthrax in its early stage with nonspecific symptoms could be confused with a wide variety of viral, bacterial, and fungal infectious diseases. Progression over 2-3 days with the sudden development of severe respiratory distress followed by shock and death in 24-36 hours in essentially all untreated cases eliminates diagnoses other than inhalation anthrax. The presence of a widened mediastinum on chest X ray, in particular, should alert one to the diagnosis. Other suggestive findings include chest-wall edema, hemorrhagic pleural effusions, and hemorrhagic meningitis. Other diagnoses to consider include aerosol exposure to SEB; but in this case, onset would be more rapid after exposure (if known), and no prodrome would be evident prior to onset of severe respiratory symptoms. Mediastinal widening on chest X

ray will also be absent. Patients with plague or tularemia pneumonia will have pulmonary infiltrates and clinical signs of pneumonia (usually absent in anthrax).

3. Specific Laboratory Diagnosis: *Bacillus anthracis* will be readily detectable by blood culture with routine media. Smears and cultures of pleural fluid and abnormal cerebrospinal fluid may also be positive. Impression smears of mediastinal lymph nodes and spleen from fatal cases should be positive. Toxemia is sufficient to permit anthrax toxin detection in blood by immunoassays, and such assays will be available in field-deployed laboratories (see Section III).

C. THERAPY

Almost all cases of inhalation anthrax where treatment was begun after patients were symptomatic have been fatal, regardless of treatment. Historically, penicillin has been regarded as the treatment of choice, with 2 million units given intravenously every 2 hours. Tetracycline and erythromycin have been recommended in penicillin-sensitive patients. The vast majority of anthrax strains are sensitive *in vitro* to penicillin. However, penicillin-resistant strains exist naturally, and one has been recovered from a fatal human case. Moreover, it is not difficult to induce resistance to penicillin, tetracycline, erythromycin, and many other antibiotics through laboratory manipulation of organisms. All naturally-occurring strains tested to date have been sensitive to erythromycin, chloramphenicol, gentamicin, and ciprofloxacin. In the current setting, treatment should be instituted at the earliest signs of disease with oral ciprofloxacin (1000 mg initially, followed by 750 mg po bid) or intravenous doxycycline (200 mg initially, followed by 100 mg q 12 hrs). Supportive therapy for shock, fluid volume deficit, and adequacy of airway may all be needed.

D. PROPHYLAXIS

VACCINE: A licensed, alum-precipitated, preparation of purified *Bacillus anthracis* protective antigen (PA) has been shown to be effective in preventing or significantly reducing the incidence of inhalation anthrax. Limited human data suggest that after completion of the first three doses of the recommended six-dose primary series (0, 2, 4 weeks, then 6, 12, 18 months), protection against both cutaneous and inhalation anthrax is afforded. Studies in rhesus monkeys indicate that good protection is afforded after two doses (10-16 days apart) for up to 2 years. It is likely that two doses in humans is protective as well, but there is too little information to draw firm conclusions. As with all vaccines, the degree of protection depends upon the magnitude of the challenge dose; vaccine-induced protection is undoubtedly overwhelmed by extremely high spore challenge.

In the present setting, three doses of the vaccine (at 0, 2, and 4 weeks) is recommended for prophylaxis against inhalation anthrax. Given projected stocks, two doses, 0.5 ml each, administered subcutaneously on days 0 and 14, are recommended initially. A third dose should be given 2 or more weeks after the second dose as additional vaccine becomes available. Contraindications for use are sensitivity to vaccine components (formalin, alum, benzethonium chloride) and/or history of clinical anthrax. Reactogenicity is

mild to moderate: up to 6% of recipients will experience mild discomfort at the inoculation site for up to 72 hours (tenderness, erythema, edema, pruritus), while a smaller proportion (<1%) will experience more severe local reactions (potentially limiting use of the extremity for 1-2 days); modest systemic reactions (myalgia, malaise, low-grade fever) are uncommon, and severe systemic reactions (anaphylaxis, which precludes additional vaccination) are rare. The vaccine should be stored at refrigerator temperature (not frozen).

ANTIBIOTICS: Choice of antibiotics for prophylaxis is guided by the same principles as that for treatment; i.e., it is relatively easy to produce a penicillin-resistant organism in the laboratory, and possible, albeit somewhat more difficult, to induce tetracycline resistance. Therefore, if there is information indicating that a biological weapon attack is imminent, prophylaxis with ciprofloxacin (500 mg po bid), or doxycycline (100 mg po bid) should begin. If unvaccinated, a single 0.5 ml dose of vaccine should also be given subcutaneously. Should the attack be confirmed as anthrax, antibiotics should be continued for at least 4 weeks in all exposed. In addition, two 0.5 ml doses of vaccine should be given 2 weeks apart in the unvaccinated; those previously vaccinated with fewer than three doses should receive a single 0.5 ml booster, while vaccination probably is not necessary for those who have received the entire three-dose primary series. Upon discontinuation of antibiotics, patients should be closely observed; if clinical signs of anthrax occur, patients should be treated as indicated above. If vaccine is not available, antibiotics should be continued beyond 4 weeks until the patient can be closely observed upon discontinuation of therapy.

BOTULISM

A. CLINICAL SYNDROME

Botulism is caused by intoxication with the neurotoxin produced by *Clostridium botulinum*. The toxin is a protein with molecular weight of approximately 150,000, which binds to the presynaptic membrane of neurons at peripheral cholinergic synapses to prevent release of acetylcholine and block neurotransmission. The blockade is most evident clinically in the cholinergic autonomic nervous system and at the neuromuscular junction.

A biological warfare attack with botulinum toxin delivered by aerosol to the respiratory tract would be expected to cause symptoms similar in most respects to those observed with foodborne botulism.

Clinical Features: Symptoms of botulism may begin as early as 3-36 hours following exposure, or as late as several days. Initial symptoms include generalized weakness, lassitude, and dizziness. Diminished salivation with extreme dryness of the mouth and throat may cause complaints of a sore throat. Urinary retention or ileus may also occur. Motor symptoms usually are present early in disease; cranial nerves are affected first with blurred

vision, diplopia, ptosis, and photophobia. Bulbar nerve dysfunction causes dysarthria, dysphonia, and dysphagia. This is followed by a symmetrical, descending, progressive weakness of the extremities along with weakness of the respiratory muscles. Development of respiratory failure may be abrupt.

On physical examination, the patient is alert, oriented, and afebrile. Postural hypotension may be present. Ocular findings may include ptosis, extraocular muscle paralysis, and fixed and dilated pupils. Mucous membranes of the mouth may be dry and crusted. Neurological examination shows flaccid muscle weakness of the palate, tongue, larynx, respiratory muscles, and extremities. Deep tendon reflexes vary from intact to absent. No pathologic reflexes are present, and the sensory examination generally is normal (although reports suggest that obtundation or sensory involvement may sometimes occur).

B. DIAGNOSIS

1. Routine Laboratory Findings: Routine laboratory findings are of no value in diagnosis. The cerebrospinal fluid is normal.

2. Differential Diagnosis: The occurrence of an epidemic with large numbers of afebrile patients with progressive ocular, pharyngeal, respiratory, and muscular weakness and paralysis hints strongly at the diagnosis. Single cases may be confused with various neuromuscular disorders such as atypical Guillain-Barré syndrome, myasthenia gravis, or tick paralysis. The edrophonium (tensilon) test may be transiently positive in botulism. Other considerations include enteroviral infections; but in these patients, fever is present, paralysis is often asymmetrical, and the cerebrospinal fluid is abnormal. In the present setting, it will be necessary to distinguish nerve-agent and atropine poisoning from botulinum intoxication. Briefly, organophosphate nerve agent poisoning results in miotic pupils and copious secretions. In atropine poisoning, the pupils are dilated and mucous membranes are dry, but central nervous system excitation with hallucinations and delirium is present. See Section IV for a more comprehensive differential.

3. Specific Laboratory Diagnosis: Detection of toxin in serum or gastric contents from cases of foodborne botulism is often feasible by mouse inoculation. In the case of inhalation botulism, toxin may well be cleared from the blood by the time symptoms are noted. Nevertheless, serum should be obtained from representative cases for such attempts. Survivors probably will not develop an antibody response due to the small amount of toxin necessary to cause death. See Section III for details of sample collection and processing.

C. THERAPY

Respiratory failure secondary to paralysis of respiratory muscles is the most serious complication and, generally, the cause of death. Reported cases of botulism prior to 1950 had a mortality of 60%. With tracheostomy and ventilatory assistance, fatalities should be <5%. Intensive and prolonged nursing care may be required for recovery (which may take several weeks or even months).

ANTITOXIN: In isolated cases of foodborne botulism, circulating toxin is usually present, perhaps due to continued absorption through the gut wall. Equine antitoxin has been used in these circumstances, and is probably helpful. After aerosol exposure, it is unknown whether toxin circulates or antitoxin would be therapeutically useful after onset of symptoms. However, administration of antitoxin is reasonable if disease has not progressed to a stable state.

A human pentavalent antitoxin produced by plasmapheresis of toxoid vaccinees is available in very limited quantities. It is an Investigational New Drug (IND) and has never been tested for efficacy. Formal safety and pharmacokinetic studies are in progress. This product is useful only for highly specialized indications, and should not be considered as generally available. There is no prospect for additional human antitoxin to be produced and made available in the foreseeable future.

A "despeciated" equine heptavalent antitoxin (vs types A, B, C, D, E, F, and G) has been prepared by cleaving the Fc fragments from horse IgG molecules, leaving F(ab)₂ fragments. It is felt that this antitoxin offers an option for therapy, and stocks have been pre-positioned in the field. Its efficacy is inferred from animal studies. Use requires pretesting for sensitivity to horse serum (and desensitization for those allergic), and disadvantages include rapid clearance by immune elimination, as well as a theoretical risk of serum sickness.

D. PROPHYLAXIS

A pentavalent toxoid of *Clostridium botulinum* types A, B, C, D, and E is available under IND status. This product has been administered to several thousand volunteers and occupationally at-risk workers, and induces serum antitoxin levels that correspond to protective levels in experimental animal systems. The currently recommended schedule (0, 2, and 12 weeks, then a 1 year booster) induces solidly protective antitoxin levels in an acceptable percentage of vaccinees after 1 year. The few available data suggest that limited and transient antitoxin levels are induced after three injections; there are no data currently available to assess immunogenicity after one or two doses, although lower levels of antitoxin than those currently recommended for laboratory workers may well offer protection in a field setting.

At present, this product is available in limited quantities, and must be administered under protocol. Contraindications include sensitivity to alum, formaldehyde, and thimerosal, or hypersensitivity to a previous dose. Reactogenicity is modest, with 2-4% of vaccinees reporting erythema, edema, or induration which peaks at 24-48 hours, then dissipates. The frequency of local reactions increases with each subsequent inoculation; after the second and third doses, 7-10% will have local reactions, with higher incidences (up to 20% or so) after boosters. Severe local reactions are rare, consisting of more extensive edema or induration. Systemic reactions are reported in up to 3%, consisting of fever, malaise, headache, and myalgia. Incapacitating reactions (local or systemic) are uncommon. The vaccine should be stored at refrigerator temperatures (not frozen).

Given current and projected vaccine stocks, three or more vaccine doses (0, 2, and 12 weeks, then 1 year if possible, by deep subcutaneous injection) are recommended only to selected individuals or groups judged at high risk for exposure to botulinum toxin aerosols.

Given projected antitoxin stocks and absence of pharmacokinetic data for human and despeciated equine products, there is no indication at present for use of antitoxin as a generally available prophylactic modality.

STAPHYLOCOCCAL ENTEROTOXIN B

A. CLINICAL SYNDROME

Staphylococcal enterotoxin B (SEB) is one of several exotoxins produced by Staphylococcus aureus, causing food poisoning when ingested.

A biological warfare attack with aerosol delivery of SEB to the respiratory tract produces a distinct syndrome causing significant morbidity and potential mortality.

Clinical Features: The disease begins 1-6 hours after exposure with the sudden onset of fever, chills, headache, myalgia, and nonproductive cough. In more severe cases, dyspnea and retrosternal chest pain may also be present. Fever, which may reach 103-106° F, has lasted 2-5 days, but cough may persist 1-4 weeks. In many patients, nausea, which may be severe, vomiting, and diarrhea will also occur. Physical findings are often unremarkable. Conjunctival injection may be present, and in the most severe cases, signs of pulmonary edema would be expected. The chest X ray is generally normal, but in severe cases, there will be increased interstitial markings, atelectasis, and possibly overt pulmonary edema. In moderately severe laboratory exposures, lost duty time has been < 2 weeks, but, based upon animal data, it is anticipated that severe exposures will result in fatalities.

B. DIAGNOSIS

1. Routine Laboratory Findings: Laboratory findings are noncontributory except for a neutrophilic leukocytosis and elevated erythrocyte sedimentation rate.

2. Differential Diagnosis: In foodborne SEB intoxication, fever and respiratory involvement are not seen, and gastrointestinal symptoms are prominent.

The nonspecific findings of fever, nonproductive cough, myalgia, and headache occurring in large numbers of patients in an epidemic setting would suggest any of several infectious respiratory pathogens, particularly influenza, adenovirus, or mycoplasma. In a single biological warfare attack with SEB, cases would likely have their onset within a single day, while these other, naturally occurring, outbreaks would present over a more prolonged interval. Naturally occurring outbreaks of Q fever and tularemia might cause confusion, but

would involve much smaller numbers of individuals, and would more likely be accompanied by pulmonary infiltrates.

The dyspnea of botulism is associated with obvious signs of muscular paralysis; its cholinergic blocking effects result in a dry respiratory tree, and patients are afebrile. Inhalation of nerve agent may lead to weakness, dyspnea, and copious secretions. The early clinical manifestations of inhalation anthrax, tularemia, or plague may be similar to those of SEB. However, rapid progression of respiratory signs and symptoms to a stable state distinguishes SEB intoxication. Mustard exposure would have marked vesication of the skin in addition to the pulmonary injury (Section IV).

3. Specific Laboratory Diagnosis: Toxin is cleared from the serum rapidly and is difficult to detect by the time of symptom onset. Nevertheless, specific laboratory tests are available to detect SEB (see Section III), and serum should be collected as early as possible after exposure. In situations where many individuals are symptomatic, sera should be obtained from those not yet showing evidence of clinical disease. Most patients develop a significant antibody response, but this may require 2-4 weeks.

C. THERAPY

Treatment is limited to supportive care.

D. PROPHYLAXIS

There currently is no prophylaxis for SEB intoxication. Experimental immunization has protected monkeys, but no vaccine is presently available for human use.

CLOSTRIDIUM PERFRINGENS

A. CLINICAL SYNDROME

Clostridium perfringens is a common anaerobic bacterium associated with three distinct disease syndromes: (a) gas gangrene or clostridial myonecrosis, (b) enteritis necroticans (pig-bel), (c) clostridial food poisoning. Each of these syndromes has very specific requirements for delivering inocula of C. perfringens to specific sites to induce disease, and it is difficult to envision a general scenario in which the spores or vegetative organisms could be used as a biowarfare agent. There are, however, at least 12 protein toxins elaborated, and one or more of these could be produced, concentrated, and used as a weapon. Waterborne disease is conceivable, but unlikely. The best available speculation (based on virtually no exploratory data with which to sharpen our conclusions) is that the alpha toxin would be lethal by aerosol. This is a well-characterized, highly toxic

phospholipase C. Other toxins from the organism might be co-weaponized and enhance effectiveness. For example, the epsilon toxin is neurotoxic in laboratory animals.

Clinical Features: The clinical picture of aerosolized *C. perfringens* alpha toxin would be expected to be that of a serious acute pulmonary insult. Absorbed alpha toxin could produce vascular leak, hemolysis, thrombocytopenia, liver damage, etc. Other toxins admixed could modify the event.

B. DIAGNOSIS

Routine Laboratory Findings: Clinical laboratory findings might include anemia (due to intravascular hemolysis), thrombocytopenia, elevated serum transaminases, and hypoxia.

Differential Diagnosis: Pulmonary signs might lead to confusion with SEB initially. Liver damage, hemolytic anemia, and thrombocytopenia are not associated with SEB, and the pulmonary findings could be reversible in SEB.

Specific Laboratory Diagnosis: Acute serum and tissue samples should be collected and rapidly transported to a reference laboratory. Specific immunoassays are available; however, their utility in diagnosis of human disease is unproven.

The enterotoxin can be detected in fecal samples from human food-poisoning cases, and bacteria are readily cultured from clinical samples.

C. THERAPY

No specific treatment is available for *C. perfringens* intoxication. Humans with enteritis necroticans have been treated with antitoxin with some success.

The organism itself is sensitive to penicillin, and, consequently, this is the current drug of choice. Recent data indicate that clindamycin or rifampin may suppress toxin production, and provide superior results in animal models.

D. PROPHYLAXIS

There is no available prophylaxis for *C. perfringens* intoxication. Toxoids are being used to prevent enteritis necroticans in humans, and veterinary toxoids are in wide use.

PLAGUE

A: CLINICAL SYNDROME

Plague is a zoonotic disease caused by *Yersinia pestis*, a gram negative, non spore-forming, bacillus. Under natural conditions, humans become infected through skin inoculation (flea bite or, less commonly, direct animal contact), and only rarely via aerosol. A biological warfare attack with plague bacilli would be delivered via aerosol, or, less likely, via contaminated vectors (fleas). The clinical picture seen would depend upon the route of delivery.

Clinical Features: Three primary syndromes are described: bubonic, primary septicemic, and pneumonic. The incubation period ranges from 2 to 10 days. In bubonic plague, onset is acute and often fulminant, with high fever, systemic signs and symptoms, and exquisitely tender lymph node or nodes. The hallmark of bubonic plague, the bubo, represents lymphadenitis involving a node draining the site of inoculation. Most commonly, the primary site is inguinal, although axillary or cervical nodes may be involved. The involved nodes are swollen and tender, becoming fluctuant and necrotic. Bubonic plague may be complicated by the development of meningitis or secondary pneumonia. Onset of primary septicemic plague is similar, but without a localizing "bubo". Infection by flea bite or other cutaneous inoculation would produce bubonic or primary septicemic disease in most individuals. Primary pneumonic plague is the disease syndrome expected after an aerosol attack. After a short incubation period of 1-6 days, there is development of cough, chest pain, bloody sputum, progressive respiratory insufficiency, and toxemia. Patients with plague pneumonia are highly contagious, and should be kept in strict respiratory isolation. Although some patients with bubonic or septicemic plague may develop secondary pneumonia as the disease process evolves, large numbers of individuals with plague pneumonia almost certainly would indicate inhalation of organisms delivered via aerosol from a biowarfare attack.

B: DIAGNOSIS

Routine Laboratory Findings: Examination of bubo aspirate, sputum, or cerebrospinal fluid by gram stain will reveal numerous organisms typical morphologically of *Yersinia pestis*.

Differential Diagnosis: Bubonic plague should be suspected in large numbers of individuals with similar findings of fever, malaise, and tender lymphadenopathy. An epidemic of pneumonic plague in its early stages could be confused with tularemia, anthrax, or SEB; continued deterioration without stabilization effectively rules out SEB, while gram stain of the sputum, culture, and presence of the plague F1 antigen in blood specimens provide more specific evidence of plague.

Specific Laboratory Diagnosis: *Yersinia pestis* can be readily cultured from blood, sputum, and bubo aspirates. Presumptive diagnosis can be made by gram stain and (if available) immunofluorescent staining. Most naturally-occurring strains of *Y. pestis* produce an "F1" antigen in-vivo, which can be detected in serum samples by immunoassays available in field diagnostic laboratories.

C. THERAPY

Plague pneumonia is highly contagious. Patients should be managed in strict respiratory isolation for at least 48 hours after therapy has been initiated. Untreated bubonic plague has a case-fatality rate commonly reported as around 50%; untreated primary septicemic and pneumonic plague are invariably fatal. Streptomycin is the preferred treatment, although tetracyclines, and chloramphenicol also are highly effective if begun early (within 8-24 hours in pneumonic plague). Intramuscular streptomycin (1 gm q 12 hours), intravenous doxycycline (200 mg initially, followed by 100 mg q 12 hours), or intravenous chloramphenicol (1 gm q 6 hours) for 10-14 days are recognized as effective against naturally occurring strains. Prophylaxis for contacts of pneumonic cases with doxycycline (100 mg po bid for 10 days) is necessary to prevent secondary transmission.

D. PROPHYLAXIS

Vaccine: A licensed, formalin-killed *Y. pestis* vaccine is marketed in the U.S., and has been utilized by U.S. military personnel for many years in highly plague-endemic areas. Vaccine efficacy remains formally unproven, although anecdotal experience suggests it is effective against, at least, bubonic disease. Reactogenicity is moderately high, and immunity acquired after a 3-dose primary series (0,1, and 4-7 months) is sustained only with boosters every 1-2 years. Live-attenuated vaccines produced in other countries are generally regarded as highly reactogenic, with a potential for reversion.

TULAREMIA

A. CLINICAL SYNDROME

Tularemia is a zoonotic disease caused by *Francisella tularensis*, a small, non spore-forming gram negative bacillus. Humans acquire the disease under natural conditions through inoculation of skin or mucous membranes with blood or tissue fluids of infected animals, or bites of infected deerflies, mosquitoes, or ticks. Less commonly, inhalation of contaminated dusts or ingestion of contaminated foods or water may produce clinical disease. A biological warfare attack with *F. tularensis* delivered by aerosol would primarily cause

typhoidal tularemia, a syndrome expected to have a case-fatality rate which may be higher than the 5-10% seen when disease is acquired naturally.

Clinical Features: A variety of clinical forms of tularemia are seen, depending upon the route of inoculation and virulence of the strain. Since the infectious dose is low (1-10 organisms by aerosol or intradermal routes), ulceroglandular, typhoidal, or pharyngeal forms could be seen. Ulceroglandular tularemia generally occurs about 3 days after exposure (range, 2-10 days), and manifests as regional lymphadenopathy, fever, chills, headache, and malaise, with or without a cutaneous ulcer. With typhoidal disease, the systemic clinical manifestations are similar to those seen in the ulceroglandular form, but there is no skin lesion or adenopathy. Typhoidal tularemia is the form of disease which occurs after inhalation of organisms; in this form, clinically and radiologically evident pneumonia may be significant. Three to five days following inhalation, the abrupt onset of fever, chills, headache, myalgia, and prostration are seen, with a non-productive cough. Deposition of organisms in the oropharynx may also produce a pharyngeal form of tularemia, with "ulceroglandular" -type lesions localized to the throat.

Differential Diagnosis: The clinical presentation of tularemia may be severe, yet non-specific. Differential diagnoses include typhoidal syndromes (e.g., salmonella, rickettsia, malaria) or pneumonic processes (e.g., plague, mycoplasma, SEB). A clue to the diagnosis of tularemia delivered as a biowarfare weapon might be a large number of temporally clustered patients presenting with similar systemic illnesses, a proportion of whom will have a non-productive pneumonia.

Specific Laboratory Diagnosis: Identification of organisms by staining ulcer fluids or sputum is generally not helpful. Routine culture is difficult, due to unusual growth requirements and/or overgrowth of commensal bacteria. The diagnosis can be established retrospectively by serology.

C. THERAPY

Streptomycin (1 gm q 12 hr IM for 10-14 days) is the treatment of choice. Gentamicin also is effective (3-5 mg/kg/day parenterally for 10-14 days). Tetracycline and chloramphenicol treatment are effective as well, but are associated with a significant relapse rate. Although laboratory-related infections with this organism are very common, human-to-human spread is unusual, and isolation is not required.

D. PROPHYLAXIS

A live-attenuated tularemia vaccine is available as an investigational new drug. This vaccine has been administered to more than 5,000 persons without significant adverse reactions, and is of proven effectiveness in preventing laboratory-acquired typhoidal tularemia.

The use of antibiotics for prophylaxis against tularemia is controversial.

Summary of Section II: Avoidance by way of physical protection is the most effective approach to biological warfare agent exposure. Clinical recognition of symptoms and signs in casualties may be the first indication of an attack. Patient specimens (blood, urine) should not pose a unique risk to medical personnel, although vegetative anthrax, plague, or tularemia organisms present in blood may be infectious.

SECTION III

Collection and Transport of Diagnostic Specimens for Definitive Diagnosis

A. Specimens to be Obtained.

1. For Routine Clinical Laboratory

a: Anthrax. Blood culture with routine media will readily detect *Bacillus anthracis*. Impression smears taken from infected mediastinal lymph nodes and spleen, smears from blood, pleural fluid, and abnormal cerebrospinal fluid (CSF) should all be positive by Gram or Giemsa stains. Positive smears and cultures should be retained for transport to the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID).

b: Botulinum toxin. None appropriate.

c: Staphylococcal enterotoxins. None appropriate.

d: *Clostridium perfringens*. Bacteria can be cultured from clinical specimens using anaerobic techniques. Positive cultures should be retained for transport to USAMRIID.

e: Plague. Blood culture with routine media will readily detect *Yersinia pestis*. Impression smears or aspirates of bubos, and smears from blood, CSF, or sputum all should be positive by gram stain. Positive smears and cultures should be retained for transport to USAMRIID.

f: Tularemia. *Francisella tularensis* is a fastidious bacterium, generally requiring specialized growth media. Suspicious isolates should be retained for transport to USAMRIID.

2. For Special Diagnostic Laboratories.

a: Anthrax. Acute serum (at least 3 ml) should be collected as early as possible after onset of symptoms, and shipped frozen to a reference laboratory (see below). Convalescent samples should be obtained from survivors and other members of the attacked unit 3-4 weeks later.

b: Botulinum toxin. Acute serum (at least 20 ml blood) should be collected as early as possible after onset of symptoms, and shipped frozen to a reference laboratory (see below). Exposed persons who are not yet symptomatic should also be bled (20 ml of blood).

c: Staphylococcal enterotoxins. Acute serum (3 ml) should be collected as soon as possible after onset of symptoms. Exposed persons who are not yet symptomatic should also be bled (3 ml). Convalescent sera from survivors and nonaffected unit members should be obtained 2-4 weeks later. Serum should be shipped frozen to a reference laboratory (see below).

d: *Clostridium perfringens*. Same as for staphylococcal enterotoxins, above.

e: Plague. Acute serum (at least 3 ml) should be collected as early as possible after symptom onset and shipped frozen to a reference laboratory (see below).

Convalescent samples should be obtained from survivors and other members of the attacked unit 3-4 weeks later.

f: Tularemia. Same as for plague (above).

3. Autopsy Samples

All tissue samples should be collected in duplicate aliquots: one (25-50 gm) to freeze for microbiology/toxicology and one in formalin for histopathology. Organs sampled should include lung, mediastinal lymph nodes, spleen, and liver. Obvious lesions and adjacent normal tissue should be taken from affected areas in any organ.

Postmortem blood (up to 20 ml) should be obtained and submitted as serum and clot/cells.

Each container should be labeled with name, SSN, and date of collection. Include a brief description of illness and gross autopsy findings; place, date, and time of death; place, date, and time of collection; prosector and unit.

Samples for analysis should be kept as cold as possible, preferably frozen. Formalin-fixed material must not be frozen.

C. Specimen Handling and Shipment

1. Specimen Handling.

a: Processing. All specimens from suspected biological warfare casualties should be submitted through the routine diagnostic laboratory chain for processing. Samples must be clearly marked for special diagnostic testing, and chain-of-custody procedures maintained.

b: Labeling. All serum samples should be completely labeled with patient's name, SSN, unit, date, and medical facility to receive results. Routine laboratory slips should be included with each sample. Data on laboratory slips should include number of disease days and the reason that samples were obtained.

c: Packaging. Serum should be contained in plastic screw-cap vials, which are securely sealed. If possible, each serum sample should be individually placed in a second plastic vial or zip-lock bag to prevent leakage. All specimens should be contained in a metal shipping can or other secondary container. Sufficient absorbent material should be packed to prevent leakage outside the container. The entire contents should be placed in an insulated shipping container with cold packs or dry ice.

d: Addresses. It is the responsibility of the laboratory officer, in concert with the physician, to ensure that suspect specimens are submitted correctly and expeditiously to a special diagnostic laboratory. These specialized testing/reference laboratory facilities will be available at several locations; the facility appropriate for a given unit or location will be guided by unit SOP. Sites established as of this writing include the following:

1. Naval Medical Unit

C/O NAVCENT Surgeon
COM USNAVLOGSUPFOR//N-9//
Bahrain
TEL: COM 011-973-728-877

**2. Army Medical Laboratory
996 General Laboratory
C/O ARCENT SURGEON
Saudi Arabia
TEL: COM 011-966-1-471-7777**

**3. USAMRIID (ATTN: SGRD-UID-E)
Fort Detrick
Frederick, MD 21702-5011
TEL: AV 343-7193/7244
COM 301-663-7193/7244
FAX: COM 301-663-2492**

**If specific questions arise regarding specimen collection, processing, or shipment,
contact USAMRIID (above) for instructions.**

SECTION IV

TABLE I
DIFFERENTIATION AMONG NERVE AGENT, ATROPINE,
AND BOTULINUM INTOXICATIONS

	BOTULINUM TOXIN	NERVE AGENT	ATROPINE
Sensorium	Usually normal	Disorientation, agitation, coma, seizures	Disorientation, excitation, agitation, irritability, coma
Ophthalmologic Abnormalities	Dilated and fixed pupils, distorted blurred vision, ptosis, extraocular muscle paralysis	Constricted pupils, dim vision (if vapor or aerosol exposure), little if any change if exposed via skin	Weak effects if usual doses given causing pupillary dilation and paralysis of accommodation
Paralysis	Flaccid paralysis. Early bulbar signs (dysphonia, dysphagia) descending to upper and lower extremities. Respiratory failure.	Rigid paralysis with twitching, jerking. Seizures.	None of significance
Autonomic Findings	Dry mouth and skin, constipation, ileus, urinary retention. Early emesis and diarrhea after food ingestion.	Excess salivation, increased sweating, involuntary defecation and urination. Severe rhinorrhea and bronchoconstriction occur if exposure is by inhalation.	Dry mouth and skin, constipation, ileus, urinary retention. Early emesis and diarrhea after food ingestion.
Onset	3-36 hours by inhalation exposure. Not absorbed through intact skin; 12-24 hours onset by oral exposure	1-10 minutes by inhalation exposure; 1-2 hours by dermal exposure	Minutes after injection, can be exacerbated by dehydration and heat exposure

PARALYSIS IN THE BW/CW SETTING

The differential diagnosis must include both botulinum and nerve agent intoxications.

a: Nerve agent is rapid in onset (minutes to 1-2 hr). A rigid paralysis develops with parasympathetic excess (salivation, miosis, sweating, involuntary defecation, and urination); central nervous system dysfunction and death soon follow. If exposure is by aerosol or vapor, constricted pupils, rhinorrhea, and bronchoconstriction also occur.

b: Botulinum toxin is slower in onset (3 hr to several days). Descending paralysis (bulbar to extremities to respiratory) and parasympathetic blockade (dry mouth, pupillary dilation, constipation, urinary retention, absence of sweating) are characteristic. Paralysis, nausea, vomiting, and diarrhea may, however, occur after exposure to either nerve agent or botulinum toxin. Central signs (confusion, seizure, coma) are rare after botulinum, but common after nerve agent intoxication.

c: Anticholinergics such as atropine can, of course, cause central nervous system changes such as agitation, confusion, and hallucinations as well as dry mouth, dry skin, and constipation. These changes could easily obscure the correct diagnosis in a soldier who used his injector even without exposure to an agent.

TABLE II

CLINICAL DIFFERENTIAL OF TOXIN AND CHEMICAL AGENTS WITH DOMINANT PULMONARY EFFECTS AFTER AEROSOL EXPOSURE

	SEB	MUSTARD (MD)	BOTULINUM TOXIN	NERVE AGENT
Onset	1-2 hours	4 hours for low dose 1 hour for high dose	3-36 hours	Minutes to 1 hour
Eye Effects	Mild conjunctivitis purulent, lasts 1-2 days	Mild to severe corneal injury and conjunctivitis lasting weeks, marked edema, vesication if higher dose exposure	Pupillary dilation associated with dry mouth, no rhinorrhea	Pupillary constriction, conjunctival hyperemia, associated with severe rhinorrhea
Respiratory Tract Symptoms	Chest pain, cough, shortness of breath	Hoarseness, nocturnal cough, progressing to productive cough with bronchitis	Shortness of breath, no wheezing or bronchorrhea	Wheezing, bronchorrhea
Neurologic	None other than malaise	Central nervous system impairment only if very high dose	Flaccid paralysis with bulbar signs (dysphonia, dysphagia)	Rigid paralysis with muscle twitching
General Symptoms	Early malaise, myalgia, fever, headache	Late fever	No fever in absence of complications	No fever in absence of complications
Gastro-intestinal	Nausea, vomiting, diarrhea prominent	Nausea, and vomiting present in higher doses but relatively mild	Can have early vomiting and diarrhea with oral exposure	Involuntary defecation
Radiologic Findings	Pulmonary edema, patchy infiltration if moderate to severe exposure	Early bronchitis without radiologic change, pneumonic complications late	None without complications	None without complications